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Original ARTICLES

ADENOMA OF THE ISLETS OF LANGERHANS: A CASE REPORT

Michael C. Govostis, M. D., Orville F. Bonnett, Jr., M. D.
and John Van Prohaska, M. D.
Chicago, Illinois

It is worthy of note that since 1927, when Wilder first reported an islet cell tumor of the pancreas, there have been approximately 300 cases (1, 3, 4, 6, 7) recorded in the literature. Microscopically many of these tumors do not fall into classifications of benign or malignant, but are reported by various pathologists as questionably malignant. This is of paramount importance to the surgeon. In some cases a malignant tumor situated in the pancreas requires the radical operative procedure of pancreaticoduodenectomy, providing of course, that it has not already metastasized. The magnitude of this procedure prevents its execution for a benign adenoma.

Some of the tumors reported as questionably malignant have pursued the post-operative course of a benign neoplasm (2, 5, 8). The impression gained from a survey of the literature is that the criteria for malignancy has not been clearly defined in this type of tumor. Our own case adds another instance of an islet cell tumor which microscopically presented evidence of invasion, but grossly appeared benign and subsequently has behaved as such.

E. P., a 38-year-old housewife, of German birth, was admitted to the Chicago Memorial Hospital on August 1, 1948, in a semi-comatose condition. The initial history was given by her husband.

For the previous nine months the patient had been experiencing periods of unconsciousness lasting from two to twelve hours, at intervals of three to four weeks. Prior to this time she had been perfectly well. Thirty hours before admission she began to perspire freely, complained of being hungry, and shortly thereafter lapsed into coma. This was accompanied at the outset by a generalized convulsion, foaming at the mouth, and urinary incontinence.

Further inquiry revealed that the patient had not gained or lost weight recently. Her appetite had been good and bowel habits normal. There was no history of subjective gastrointestinal disturbance. The cardiovascular, respiratory, and genito-urinary systemic inquiries were essentially negative.

She had had the usual childhood illnesses, but had never been seriously ill or had previous surgery. The menstrual history was normal. Her habits were normal and she denied the use of drugs, alcohol, and tobacco. She had two children, both of whom were well. The family history was negative except for an instance of schizophrenia in a maternal aunt.

Physical Examination: Revealed a semi-comatose, dehydrated, obese, white woman who moved her left arm slightly in response to painful stimuli. Her temperature was 100°F., rectally; pulse, 88 per minute; respirations, 18 per minute; and blood pressure, 120/80. The extremities were flaccid.

Examination of the head and neck revealed no abnormality. The pupils were 3 millimeters in diameter, equal, and round. They reacted normally to light. The optic discs were normal and both corneal reflexes were present. There was no muscle rigidity. The thyroid gland was normal on palpation. The breasts were large and pendulous. The heart, lungs, abdomen,

pelvis, rectum, and extremities were normal. Thorough neurological examination revealed no other abnormal findings.

A blood sugar, drawn on admission, was 10 milligrams per cent. An intravenous infusion of 1000 cubic centimeters of 5 per cent glucose in physiological saline was given and the patient rapidly became alert and cooperative. Another blood sugar at this time was 137 milligrams per cent. The Kahn and Wassermann tests of blood and spinal fluid were negative. The urinalysis revealed four-plus acetone. The blood count was: Erythrocytes, 4,700,000; hemoglobin, 86 per cent; white blood cells, 6,150; and normal differential count. The spinal fluid had the normal number of cells, a total protein of 26 milligrams per cent, a negative Pandy test, a colloidal gold curve of 0000000000, and a sugar level of 8 milligrams per cent (taken when patient was in hypoglycemic shock).

The next day the patient was fasted in preparation for an upper gastrointestinal roentgenologic study. She became comatose and the blood sugar at this time was 40 milligrams per cent. She immediately responded to 20 cubic centimeters of 50 per cent glucose given intravenously. Glucose tolerance tests were done pre-operatively and post-operatively, and are shown in graphic form in Fig. 1.

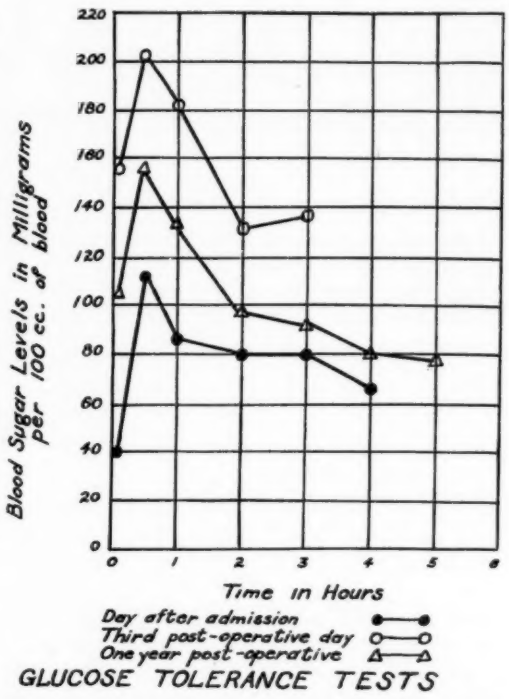

Fig. 1. Graph showing pre-operative and post-operative Glucose Tolerance Curves.

Fluoroscopic barium studies revealed no abnormality in the esophagus, stomach, or duodenum. The duodenal curve was within normal limits. A roentgenogram of the chest was normal.

On the sixth hospital day (an early morning blood sugar was 48 milligrams per cent) the patient was taken to the operating room and the abdomen opened through an upper right paramedian incision. The liver, spleen, gall bladder, stomach, bowel, and pelvic organs were normal. Upon further examination a tumor was found in the head of the pancreas lateral to the second portion of the duodenum. The gastrocolic omentum was then opened and the body and tail of the pancreas explored. No other tumors were found. The opening in the gastrocolic ligament was closed. The lateral peritoneum of the duodenum was incised and the duodenum reflected medially. The tumor lay near the surface of the pancreas and measured approximately 1.5 centimeters in each of its three dimensions.

By blunt and sharp dissection the tumor was extirpated. The dissection in the pancreas was done between clamps and all points ligated with silk. The defect in the pancreas was then closed with interrupted silk sutures and the entire area peritonealized. A penrose type drain was placed in the region of the head of the pancreas and brought out through the abdominal wound. The abdomen was closed by layers. The operative procedure was uneventful and the patient received 1000 cubic centimeters of 5 per cent glucose in water and 500 cubic centimeters of whole blood while in the operating room.

During surgery a frozen section of the tumor was made, proving it to be an islet cell adenoma. Photomicrographs of the fixed speciment, under low and high power, are shown in Figures 2 and 3. The pathologist's final report was as follows:

"Adenoma of the Island of Langerhans, with hyalinization.

"Note: The tumor is invasive but shows no evidence of anaplasia.

"*Gross Description*: The speciment consisted of a portion of previously fixed tissue, averaging 1 x 1 x 1 centimeters. Cut section revealed a

lobulated grey-tan granular surface. Small yellow punctate areas were visible throughout the cut section.

"*Microscopic Description*: Sections through the tumor reveal round and oval cells with uniform hyperchromatic nuclei, the latter containing punctate chromatin and having lightly neutrophilic homogenous cytoplasm. The cells radiate from fibrous connective tissue with hyalinized strands in which sclerosed blood vessels are apparent. Mallory's ozan stain reveals the stroma to be densely blue. The cells have finely granular neutrophilic or purple-grey cytoplasm. An occasional cell has apparently basophilic cytoplasm. These cells in one focus extend from the capsule and copress surrounding tissue."

Six hours after the operation the patient's blood sugar was 132 milligrams per cent. On the third post-operative day the patient complained of severe epigastric pain. A serum amylase was found to be 381 units. The drain was removed on the fourth post-operative day. Immediately there was a profuse sanguino-purulent discharge from the drain site. A culture showed the infecting organisms to be Escherichia coli and aerobacter aerogens. The infection was readily controlled by penicillin and streptomycin therapy and the drainage became clear in a few days. It then became evident that the patient had a pancreatic fistula. The discharging fluid was analyzed for pancreatic enzymes and was found to contain 8,160 units of amylase and 1.560 units of lipase per hundred cubic centimeters. A catheter was inserted into the fistulous opening and continuous suction applied.

Further progress was uneventful. The patient was discharged on the twenty-first post-operative day. At this time there was only a slight drainage from the pancreatic fistula. When the patient returned home and resumed a more liberal diet she reported that the drainage increased in volume. This was noted particularly post-prandially and lasted from one to two hours. She was placed on a milk diet and we noted that the fistula drained very little. Two months from the time of surgery it had healed.

Following surgery a specimen of urine was collected every four hours for the first four days and every six hours thereafter. Qualitative examination of these specimens revealed 1-plus to 3-plus reduction for glucose and on occasions a trace of acetone. During the last week of hospitalization neither acetone nor sugar were found in the urine. At no time did the patient receive insulin.

Three months after discharge the urine was found negative for reducing substances. The fasting blood sugar was 160 milligrams per cent.

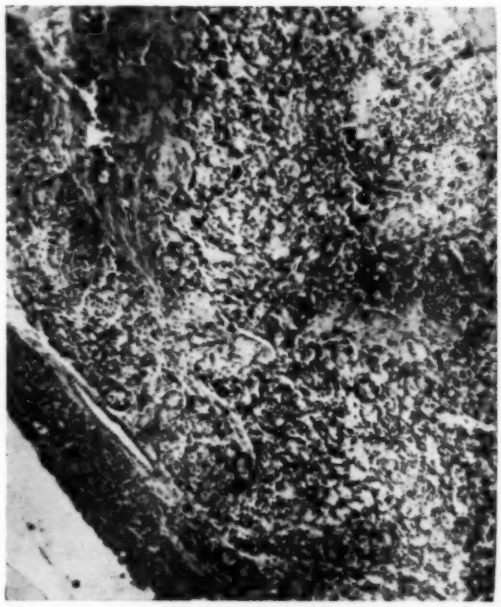

Fig. 2 Adenoma of the Islets of Langerhans. Note the Invasive Character of the Tumor. (Photomicrograph X100)

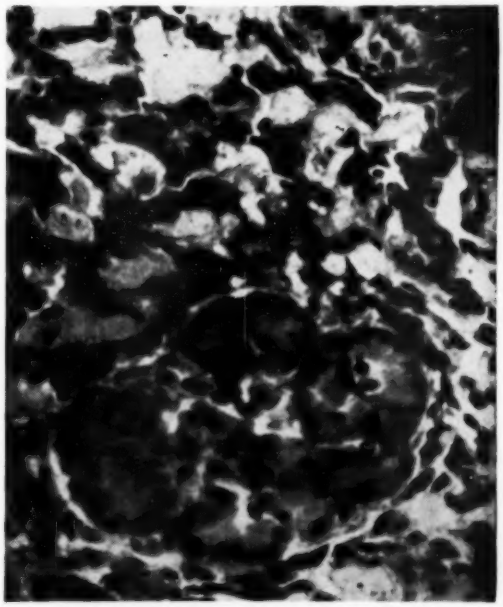

Fig. 3. Adenoma of the Islets of Langerhans. (Photomicrograph X200)

A glucose tolerance test was not done at this time.

On August 1, 1949, one year after the previous admission, the patient was re-admitted to the hospital. At this time she complained of attacks of dizziness and weakness, of two weeks' duration. These attacks were entirely unrelated to food intake nor were they precipitated by fasting. She was confused, anxious, and stated that she was worried and "had terrible ideas in her mind." At this time physical and laboratory examinations were normal.

These examinations indicated, beyond any doubt, that there was no evidence of recurrence of hyperinsulinism. The patient was discharged from the hospital with the diagnosis of psychosis.

COMMENT

In reviewing the literature it became evident that the criteria for malignancy in the islet cell tumor must be re-evaluated. Many cases are ported as questionably malignant and subsequently prove to be benign. Ours was such a case.

The psychosis which developed in this patient is interesting. One other report of a similar complication was made by Sandbloom(9). He reported a case of proved islet cell adenoma in which the patient subsequently developed a dementia and epileptiform seizures. It is difficult to believe however that the psychosis developed in this patient one year after surgery was brought on by cortical damage in one of her hypoglycemic states. The pancreatic fistula was a troublesome complication. We believe that a mild continuous suction of the fistula, protection of the skin with aluminum paste, and milk diet were responsible for early healing. We observed repeatedly in this case that a milk diet reduced the secretion of pancreatic juice.

SUMMARY

1. A proved case of islet cell adenoma is presented.

2. This presentation suggests that in some instances the histological criteria of malignancy or suspected malignancy of islet cell tumors are not firmly established.

3. A second observation of the development of psychosis following the surgical cure of hyperinsulinism is noted.

4. A substantial reduction of the flow of pancreatic juice through a fistula was noted when a normal diet was replaced by a meat-free milk diet.

REFERENCES

1. F. N. Allan & S. F. Marshall—Surgical Treatment of Islet Tumors With Hyperinsulinism—Surg. Cl. of N. A., 25:719-725, June 1945.
2. L. C. Carpenter, Jr.—Hypoglycemia, Secondary To Insular Adenoma, With Report Of Case—Jour. Mich. Med. Soc., 45:70-72, Jan. 1946.
3. R. M. Clyne, H. M. Leeds, & J. S. Cowdry—Review Of Lit. Spontaneous Hypoglycemia Due To Islet Cell Tumors—N. Y. St. Jour. Med. 45:405-409, Feb. 15, 1945.
4. V. K. Frantz—Adenomatosis of Islet Cells With Hyperinsulinism—Ann. Surg., 119-824-844, June 1944.
5. M. Haines—Islet Cell Tumor—Jour. Path. & Bact., 58:104-107, Jan. 1946.
6. P. F. A. Hoefer, S. A. Gutman, & I. J. Sands—Convulsive States and Comas In Cases of Islet Cell Adenoma—Am. Jour. Psych, 102:486-495, Jan. 1946.
7. R. Lopez-Krueger, M. Dockerty—Tumors Of the Islets of Langerhans—S. G. & O., 85:495-511, 1927-1945.
8. J. Rabinovitch & S. Achs—Adenoma Of the Islets of Langerhans—Arch. Path., 40:74-77, July 1945.
9. P. Sandblom—Spontaneous Hypoglycemia: Report of Seven Cases—Act. Med. Scand., Supp. 196:45-62.

PERIODIC PARALYSIS ASSOCIATED WITH EXOPHTHALMIC GOITER

Howard D. Cogswell, M. D. and Lindsay E. Beaton, M. D.
Tucson, Arizona

Periodic paralysis is a rare disease. It is characterized by attacks of flaccid paralysis of the somatic musculature below the neck, occurring at irregular intervals, loss of electrical and mechanical excitability with loss of the deep tendon reflexes of the involved muscles, and absence of sensory or psychic disturbances. In the intervals between attacks the patient may experience weakness or stiffness in the muscles but otherwise apparently is in normal health. Muscles innervated by the cranial nerves are seldom affected and sphincteric control is preserved. The episodes of paralysis are more prone to appear after prolonged periods of rest or during sleep and are noted frequently on waking in the morning. The attacks may be precipitated by a high carbohydrate meal,(1), exposure to cold(2), or emotional upsets. As in all chronic paroxysmal diseases, it is difficult to evaluate the significance of these precipitating factors. The paralysis usually starts in the periphery of the limbs, the legs most commonly, and advances proximally; the length of its persistance varies from a few hours to several days followed by recession of the paralysis in a reverse order to that in which it came on. The heart may show dilation of the left ventricle, a transient murmur in the mitral area, tachy-

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cardia(3), and changes in the electrocardiogram (4), during an attack.

It would seem, from reviewing the literature, that there are at least two types of periodic paralysis. The first and more common is the familial periodic paralysis which occurs as a familial inherited trait behaving as a Mendelian dominant from generation to generation with varied manifestations. Its usual onset is in the first or second decade of life occurring in males three times as commonly as in females. The second and rarer type is the periodic paralysis associated with exophthalmic goiter. This is sporadically seen occurring almost entirely in young adult males.

Most authors reporting on this subject include the two types as one or the same entity. It is quite probable that a common factor is present in both types to produce the paralysis. Since, however, there are definite physical and pathological findings with curative therapy available for the paralysis associated with hyperthyroidism and none of these that are constant in the familial type, it would seem apparent that there are in reality two diseases producing periodic paralysis as a pathognomonic sign.

The following illustrates the typical symptoms with a cure affected by a sub-total thyroidectomy in an individual affected by hyperthyroidism associated with periodic paralysis:

Report of Case: G. E., a Mexican male musician, aged 36 years, entered the hospital on March 31, 1947. Until 1941 this patient had enjoyed normal health. During the mid-portion of that year he experienced attacks of 'paralysis' on several occasions, at which time he had been unable to move his lower extremities. These attacks had lasted several hours, gradually subsiding, and the only residual the following day was generalized muscle weakness. The attacks subsided completely in the next few months and did not make their reappearance until two months before admission to the hospital. He was first seen by a physician in January, 1947, complaining of paralysis in the legs and shoulder girdles. This had its onset after the patient had eaten a heavy meal and the paralysis persisted about four hours. During the previous four months he had lost thirty pounds in weight and experienced episodes of epigastric pain associated with abdomnal distention, sweating, nervousness and itching of the skin. Physical examination the next morning revealed the following positive findings: blood pressure 110/80; pulse 110; moderate exophthalmus; marked tremor of the hands and fingers; an enlarged symmetrical thyroid gland; absent deep reflexes; spasticity of the ankles and marked weakness of all extremities. A rectal examination was attempted, but, due to the extreme sensitivity of the patient, this was not possible. X-rays of the gastro-intestinal tract and chest were normal. The basal metabolic rate was plus 94 per cent.

The patient was started on propylthiouracil, 50 mg., three times a day; iron; phenobarbital, and vitamin B complex with gradual improvement. During the pre-hospital period he experienced several episodes of weakness of the shoulder girdles and lower extremities but no definite paralysis. He had gained 29 pounds before his entrance to the hospital. Physical examination at the time of his hospital admission showed the following changes from the examination two months previously: blood pressure 126/80; pulse 80. The exophthalmus had lessened; the tremor of the hands was absent; deep reflexes were diminished but present; the ankle spasticity had disappeared; rectal examination was possible and the sphincter action was normal. The basic metabolic rate was minus 13 per cent. The complete blood count was normal as was the urinalysis. The serology was negative.

A subtotal thyroidectomy was performed on April 2, 1947. His convalescence was uneventful and he left the hospital on April 9, 1947, on the seventh postoperative day. He was last seen in December, 1951. At this time he stated that he was well. He had gained 40 pounds since his operation, had experienced no further attacks of weakness or paralysis, and was working as a musician nightly.

Very little is known regarding the etiology of this disease and no constant pathological findings have been present on the few postmortem examinations that have been made. It has been found that low levels of serum potassium existed during an attack of both types of periodic paralysis (hyperthyroidism or familial, (5). In some instances the attacks could be lessened or terminated by the administration of potassium salts. McQuarrie(6) and others found that lowering the blood potassium by various methods induced attacks in some susceptible individuals. Attacks induced by epinephrine, intravenous glucose, or desoxycorticosterone definitely estab-

lished the fact that the concentration of serum potassium falls sharply during such attacks. A disturbance of the potassium metabolism is apparently not the basic cause of the condition per se, however. Very low values for serum potassium are found in other diseases in which the distinctive phenomena of periodic paralysis are not present.

Shinoski(1) believed that periodic paralysis is a polyglandular disease. He observed 24 cases of periodic paralysis, seven of which were associated with exophthalmic goiter. He noted a definite increase in the frequency and severity of the attacks of paralysis following the administration of thyroid extract in 6 of the 7 cases of hyperthyroidism. It seems improbable that all cases of periodic paralysis are due to a polyglandular disease as many have shown no glandular dysfunction whatever.

Autointoxication has been suggested by many investigators(7). Examinations of body secretions, excretions, and metabolism have been made, always with the object of finding the evasive toxin. No convincing supporting evidence has been discovered. Findings which are fairly constant during a paralytic episode are: an increase of oxygen consumption(8), elevation of the lactic acid concentration in the blood(9), a lowering of the blood phosphorus(6), and a low serum potassium(5).

The oxygen consumption of pieces of excised muscle taken from a patient with familial periodic paralysis was compared to the oxygen consumption of muscle taken from a normal person(10). Whereas the muscle from the patient consumed 5.3 cu. mm. of oxygen per gram per minute, the specimen from the normal subject consumed 9.1 cu. mm. respectively. The same pieces of muscle were analyzed for total inorganic and organic acid soluble phosphorus, phosphocreatine, and creatine. The content of these substances was found to be considerably lower in the patient's muscle than that of the control, except that the phosphocreatine was slightly increased. These observations are significant but await confirmation.

Periodic paralysis associated with hyperthyroidism is cured by inhibiting the function of the thyroid gland. Seed(11) controlled the symptoms in a patient by the administration of 6-propylthiouricil; complete relief resulted following roentgen therapy to the thyroid gland and administration of iodine in a case observed by Dunlap and Kepler(12), and a number of cures have been reported following subtotal thyroidectomy(3),(12), and (13). In some instances a recurrence of the hyperthyroidism has been accompanied by episodes of periodic paralysis. It is known that patients affected by exophthalmis goiter frequently display muscle weakness, quadriceps weakness being one of the disease's diagnostic findings. Weakness in the bulbar group of muscles, manifesting difficulty in deglutation and phonation, ocular palsy or ptosis may all be associated with exophthalmic goiter. There is a type of myasthenia gravis which is sometimes associated with thyrotoxicosis(14). It seems apparent that there is some physiologic or chemical change, at present not understood, which occurs in muscle tissue in cases of exophthalmic goiter which is responsible for the production of the various myopathies.

Many writers have claimed an antagonism between the thyroid and thymus glands. The fact that the thymus is usually persistent in patients with exophthalmic goiter has been advanced in support of such a hypothesis(15). One of Shinoski's patients suffering from periodic paralysis associated with hyperthyroidism died, and the autopsy showed no anatomical changes except in the thyroid and thymus glands, which were both enlarged. It is interesting to speculate on the possible relationship between the thymus gland and thyrotoxicosis associated with periodic paralysis. The relief of muscle weakness and paralysis following the removal of a thymus gland in myasthenia gravis is akin to the recovery following thyroidectomy for exophthalmic goiter with paralysis. Many of the findings differ in the two diseases. Prostimine, a valuable aid in myasthenia gravis, had no beneficial effect when administered to a patient in an attack of periodic paralysis(11), yet the fact that the thymus is related to muscle weakness and paralysis and is usually present in exophthalmic goiter is a factor which should bear more investigation in establishing the etiology of this interesting and rare disease.

BIBLIGRAPHY

1. Shinosaki, T., Ztschr, T. D., Qes. Neurol. Psychiat. 100: 564, 1926.
2. Schoenthal, L., Amer. Journ. Dis. of Child., 48:799, 1934.
3. Hildebrand, A. G., and Kepler, E. J., Journ. Nerv. and Mental Dis., 94:713, No. 6, 1941.
4. Stewart, H. J., Smith, J. J., and Milhorat, A. T., Am. J. Med. Sci., 199:789, 1940.
5. Biemond, A., and Daniels, A. P., Brain, 57:91, 1934.
6. McQuarrie, I., Annual Clinical Conf. Chicago Med. Society, March, 1947.
7. Morrison, S., and Levy, M., Archives of Neur. and Psychiat., 28:386, 1932.
8. Edsall, D. L., and Means, J. H., Am. J. Med. Sci., 150:169, 1915.
9. Kirk, E., and Moller, E., Acta. Med. Scand., 80:64, 1933.

10. Victor and Wolf (Quoted from Schoenthal).
11. Seed, L., West. Journ. of Surg., Obst. and Gyn., 55:640, Dec. 1947.
12. Dunlap, H. F., and Kepler, E. J., Endocrinology, 15:541, 1931.
13. Mora, J. M., Endocrinology, 16:407, 1932.
14. Brain, R. W., Quart. J. Med. 7, 293:1938.
15. Means, J. H., The Thyroid and Its Diseases, 2nd Edition Pg. 104, J. B. Lippincott Co., Philadelphia, Pennsylvania.

SUDDEN DEATHS IN INFANTS

(With Reports of 4 Cases)

John Emmett, M. D.* and Maurice Rosenthal, M. D.**
Atlanta, Georgia and Phoenix, Arizona

Four cases of sudden death in infants in which epidemiological, pathological and laboratory studies were done are reported below.

In two of the cases the infants were found dead and the circumstances surrounding death suggested acidental mechanical suffocation. Had careful postmortem studies not been done, the deaths would undoubtedly have been so recorded. In the other two cases the infants were not found dead but had such rapid, fulminating illnesses as to die within a few hours after suddenly developing serious symptoms in the course of a mild "cold."

Vital statistics of the United States each year include over a thousand deaths in infants under one year of age as due to "accidental mechanical suffocation," In 1948, for example, there were 1,568 infant deaths so classified - a minimal figure, since in that year there were 5,315 deaths in infants under one year ascribed to "asphyxia, cause not specified" and several hundred deaths ascribed to "status thymicolymphaticus."

Farber(1), Abramson(2), Werne and Garrow(3,4) and others have shown that the certifications of "accidental mechanical suffocation," "status thymicolymphaticus"*** or "aspiration of stomach contents" in infants found dead or dying unexpectedly are erroneous. The serious implications inherent in the conclusion that an infant has died of a preventable accident make it imperative that careful and complete postmortem studies be done in every such case. In most of these cases the presence of a fulminating disease process will then be demonstrated and the parents of the infant spared the lifetime burden of guilt which all too frequently is imposed on them.

The cases here reported are illustrative of the problem.

CASE 1

A white male infant, 4 months of age, was found dead by his mother in the bed in which they both had slept. The child had been well the night before save for a "cold." The mother was distraught by the fear that during the night she had rolled over on the child and so smothered it. The diagnosis of accidental mechanical suffocation was entertained and would have been held had not a complete autopsy been performed and epidemiological follow-up done.

AUTOPSY REPORT: As is usual in these cases, there were no gross findings to account for death. Microsopic findings, however, were significant and revealing as described below.

BRONCHIAL TREE: The bronchial passages show swelling of the epithelium with degenerative change and desquamation into the lumen.

LUNGS: The pleura shows edema and separation of the collagenous and reticulum fibers. Interlobular septae of the lungs are edematous and the vessels congested. Alveolar spaces contain pink-staining, hyaline-like masses and a moderate number of mononuclear cells. The alveolar walls are thickened due to edema and infiltration with polymorphs, lymphocytes and plasma cells.

HEART: The epicardial surface is edematous and the vessels congested. Petechial hemorrhages are numerous in the epicardium.

KIDNEYS: The kidneys show marked congestion throughout the cortex and the medulla. The tubular epithelium presents varying degrees of cloudy swelling.

LIVER: Many of the hepatic cells present a marked degree of swelling. The sinusoids are compressed as a result of the swelling of the hepatic cells.

ARDENALS: There is increased fat content of the cortical cells with disintegration of many. Cells of the medulla also show degeneration and disintegration. Blood vessels in the cortex and medulla are congested.

SMALL INTESTINE: The ileum shows marked hyperplasia of lymphoid elements with edema and vascular congestion. There is diffuse infiltration of the intestinal wall with polymorphs,

*Communicable Disease Center, Public Health Service, Federal Security Agency, Atlanta, Georgia.
**Pathologist, Memorial Hospital, Phoenix, Arizona.
***Status lymphaticus is no longer regarded as an explanation of sudden death. It is now recognized that infants and children who die suddenly from any cause exhibit a relative enlargement of the thymus and other lymphoid structures, which is merely an expression of good nutrition. Holt and McIntosh(5).

lymphocytes and eosinophiles. The submucosa, muscularis and serosa are edamatous and the blood vessels congested.

ANATOMICAL DIAGNOSIS:

Pneumonitis, acute.
Enteritis, acute.
Congestion of liver, spleen and gastro-intestinal tract.
Petechial hemorrhages of the epicardium.

It is apparent that this infant died from an overwhelming infectious process and not from mechanical suffocation as had first been supposed. Epidemiological follow-up revealed that the child had been discharged from a hospital about three weeks previously, where he had been treated with penicillin for bronchopneumonia. After discharge the child was apparently well save for the persistence of a chronic "cold" with nasal catarrh and a productive cough.

Bacteriological study of secretions from the bronchial tree revealed a beta-hemolytic *Escherichia coli.* (See discussion.)

Sections of lung were obtained under sterile precautions, frozen and shipped to the Virus and Rickettsial Laboratories of the Communicable Disease Center, Montgomery, Alabama for isolation of a virus. This material, inoculated into three-weeks-old mice, yielded no virus.

CASE 2

A white infant, 2 months of age, was found dead in his crib by the mother on awakening in the morning. The child apparently had been perfectly well when put to bed the night before and it was assumed that he had smothered in the bedclothes during the night. To the parents' grief were added their feelings of guilt that they had allowed their child to sufficate. What would have been ascribed as a death due to accidental mechanical suffocation was correctly diagnosed because an autopsy was requested and careful pathological study was done.

AUTOPSY REPORT: No evidence of asphyxia due to mechanical suffocation was found. The lungs presented an atypical pneumonitis such as is frequently associated with a virus etiology. In addition, there was edema and congestion of the brain and congestion of the liver, spleen and intestinal tract.

ANATOMICAL DIAGNOSES:

Pneumonitis, acute atypical
Edema and congestion of the brain
Congestion of liver, spleen and gastro-intestinal tract

Cultures for virological and bacteriological study were taken despite the fact that the body had been embalmed some eight hours before. These cultures (from nasopharynx, bronchial tree, lungs and liver) revealed no organism and the nature of the fulminating infection in this case must remain obscure.

The following two cases of unexpected death in infants had such rapid courses of clinical illness leading to death that under other circumstances they might have been found dead in crib or bed. Their symptoms attracted attention, though only a few hours before death. They illustrate the presence of overwhelming infections in infants previously considered to have nothing more than mild colds.

CASE 3

A 2-months-old white female infant, previously well save for a mild "cold," was seen in the emergency room early one morning because the child had vomited her morning feeding. Examination was unimpressive and a diagnosis of an upper respiratory infection was made. An injection of penicillin was given and the child was sent home. The temperature at this time was 102.8°. Later that morning the child suffered convulsions and developed severe respiratory distress. She was returned to the hospital, became comatose and died at 2:00 P.M., about six hours after she had first become ill. A white blood cell count revealed a leucocytosis of 35,000.

It was thought at first that this was death due to aspiration of vomitus but autopsy revealed the cause of death to be an overwhelming respiratory infection.

AUTOPSY REPORT: The significant findings were in the lungs and the brain. The lungs revealed a patchy pneumonitis and congestion. All of the interstitial vessels were dilated and packed with red cells. The pleura was edematous and congested. The bronchial epithelium revealed several areas of desquamation.

The brain revealed a marked degree of edema and vascular congestion. The Virchow-Robin spaces were widened and some of the neurones revealed degenerative changes.

ANATOMICAL DIAGNOSIS:

Pneumonitis, acute
Congestion and edema of the brain
Hyperplasia of the solitary lymph follicles

and Peyer's patches of the lower ileum
Congestion of ilver, spleen and gastro-intestinal trace

This autopsy was performed within an hour after the child's death and surgical aseptic technique was used throughout. Specimens of pleural fluid, lung and enteric contents were studied for both viruses and bacteria. No virus was isolated, but bacteriological cultures revealed a beta-hemolytic *E. coli* (O-group 6) from secretions of the bronchial tree and nasopharynx.

CASE 4

A white male infant, 6 months old, died suddenly after admission to hospital early in the afternoon. He had been well that morning, had been observed playing and laughing as usual. Later in the forenoon he suddenly developed respiratory difficulty which rapidly became worse. He was admitted to the hospital but died within an hour and a half thereafter. The entire course of the illness was little more than four hours. Had it occurred at night in such circumstances as to permit the allegation of smothering by bedclothes or pillow, this death would likely have been thought due to accidental mechanical suffocation.

AUTOPSY REPORT At autopsy, significant findings were present in the lungs and brain. The lungs revealed thickened alveolar walls, congested capillaries and edema. There were many areas of patchy pneumonitis in which the alveoli were filled with mononuclear histiocytes.

The brain sections revealed a marked degree of edema as evidenced by widening of the reticulum meshwork. The capillaries were widely dilated and filled with red cells. Some of the neurones showed regressive changes.

ANATOMICAL DIAGNOSIS:
Patchy pneumonitis, etiology undermined
Enteritis, acute
Edema and congestion of the brain

Death was considered due to cute pneumonitis of undetermined etiology. Inasmuch as the body had been embalmed before autopsy, no cultures were taken in this case. Epidemiological follow-up, however, revealed that the twin sister of the dead infant had been diagnosed by the family's physician as having pneumonia in the week preceding her brother's death and that the brother had had catarrhal symptoms of what the parents considered only as a mild "cold."

DISCUSSION: There are no gross anatomical findings or definite postmortem criteria to prove asphyxial death unless the means of asphyxiation or the effects of the method used (such as skin lesions in strangulation from a wire or rope) are demonstrable. Since this is true, such certification as a cause of death is never tenable unless careful and complete postmortem studies have ruled out all other possible causes.

Werne and Garrow(3) investigated 167 infants found dead in crib, carriage or bed while in apparent health. Their conclusions bear repetition.

"In no instance has our investigation proved accidental mechanical suffocation of a healthy infant by bedclothes or in analagous manner.

"Since in 26 per cent of our gross cases autopsy findings immediately excluded death by accidental mechanical suffocation, all such certifications *without autopsy* may be considered inaccurate. Furthermore, we may consider as *unsatisfactory* all autopsies in which there was failure to examine the brain, the mastoids, the middle ears and the neck organs, in addition to the routine dissection of the thoracic and abdominal viscera. We may also discard all cases that have not had a complete microscopic examination."(3)

The fact that a beta-hemolytic *E. coli* was isolated from the respiratory passages in two of the cases here reported is of interest and has possible etiological significance.(9) Neter et al., (6) have recently summarized evidence suggesting that two types of *E. coli* (not ordinarily among the type of *E. coli* composing the normal intestinal flora) may cause infantile diarrhea. An alpha, 011, and a beta, 055, type are described and from a series of four infants who did not harbor the organism preceding illness, one or the other of these two types was recovered from feces, throat and nasopharynx during the course of subsequent diarrheal disease. *E. coli* septicemia and meningitis have been reported in the literature(7, 8) and while the type isolated from the cases of sudden death in infants described above is not the same serotype, 655, as the pathogenic type studied by Neter et al., the possibility of its etiological relationshp in these cases must be considered. Both cases, it will be recalled, revealed an enteritis at autopsy.

SUMMARY: Four cases illustrative of the problem of sudden unexpected death in infants are reported. The erroneous nature of such certifications as "accidental mechanical suffocation,"

"status thymicolymphaticus" and "aspiration of stomach contents" as causes of death in these cases is emphasized. The importance of careful and complete autopsies which will in most cases reveal evidence of a fulminating infection commonly involving the respiratory tract is pointed out. The responsibility for correct certification of sudden unexpected death in infants is shared by physician, coroner and pathologist, none of whom should make or accept the diagnosis of "accidental mechanical suffocation" until a careful and complete autopsy has been done.

REFERENCES

1. Farber, S., Unexpected Death in Early Life, New Eng. Med. Jour., 219:836, 1938.
2. Abramson, Harold, Accidental Mechanical Suffocation in Infants, J. Pediat., 25:404, Nov., 1944.
3. Werne, J. and Garrow, I., Sudden Deaths of Infants Allegedly Due to Mechanical Suffocation, Am. Jour. Pub. Health, 37:675, June, 1947.
4. Werne, J., Postmortem Evidence of Acute Infection in Unexpected Death in Infancy, Am. J. Path. and Bact., 18:759, July. 1942.
5. Holt and McIntosh, Holt's Diseases of Infancy and Childhood, 11th ed., Appleton-Century, N. Y., 1939, p. 61.
6. Neter, E., Webb, C. R., Shumway, C. N. and Murdock, M. R., Study on Etiology, Epidemiology, and Antibiotic Therapy of Infantile Diarrhea, with Particular Reference to Certain Serotypes of Escherichia coli, Am. Jour. Pub. Health, 41:1490, Dec., 1951.
7. Randall, K. J., Suppurative meningitis in Newborn due to coliform bacilli, J. Clin. Path., 1:150, May, 1948.
8. Vignec, A. J., Murphy, T. F., Vidal, I. E. and Julia, J. F. Epidemic Diarrhea of Newborn During and After Neonatal Period, Am. J. Dis. of Children, 79:1008, June, 1950.
9. Fraser, M. D., Bact. Coli Meningitis in the Newborn Lancet, 1:420, February 23, 1952.

LETTERER-SIWE DISEASE: REPORT OF A CASE*

Robert H. Snapp, M. D.
Phoenix, Arizona

Systemic reticulo-endothelial granuloma, including Letterer-Siwe disease, Schuler-Christian disease, and eosinophilic granuloma, was extensively reviewed by Laymon and Sevenants(1) in 1948. These authors emphasized the cutaneous as well as the internal manifestations which may occur in this group of diseases. There is considerable evidence that these three diseases represent variations of the same basic disorders of the reticulo-endothelial system. Letterer-Siwe disease, since it is more rapidly fatal, does not show lipids in the tissues as does Schuller-Christian disease which runs a more protracted course. Bone lesions are comparable in all three diseases, but occur more constantly in eosinophilic granuloma. The cutaneous manifestations are varied and overlapping in the three conditions. Although the following case is reported as Letterer-Siwe disease, there are some features which show its close relationship to SchulerChristian disease.

REPORT OF CASE

J. M. K., a 17 month old, white male infant, was first seen in the office in November, 1949. The chief complaint was that of a crusting, itchy eruption in the scalp of 14 months' duration. The child was born in a small mining community in northern Arizona, was premature at birth, weighing 4 lbs. 8 oz., and was placed in an incubator for 3 weeks. There were no siblings. The patient had had no previous communicable diseases and no immunizations. There was no history of familial or hereditary diseases.

The child had been given evaporated milk formula, vitamins, cereal, eggs, and meat at the usual age. He sat at 6 months and walked at 14 months, but apparently had never been well, and showed poor weight gain. At the age of 3 months the parents had noted pin-head sized, crusted, itchy spots scattered throughout his scalp. Various proprietary remedies had been applied locally for 9 months without success. Several dermatologists were consulted and the diagnosis of infantile eczema and seborrhea were considered. Various types of medications were prescribed locally, including sulfur, resorcin, ammoniated mercury ointment, boric acid compresses, and Burow's solution, each of which tended to clear the condition for a few days with sudden recurrence of the eruption in spite of continued active therapy.

Examination of the scalp revealed a rather diffuse, erythematous, scaly, crusted, papular eruption with marked thinning of the hair. When the crusts were removed a moist weeping surface was evident, without bleeding. Because of the striking seborrheic nature of the eruption one more trial was made with two percent resorcin, three percent salicylic acid, and five percent sulfur in a cold cream base.

The parents returned six weeks later giving the same story of complete regression of the eruption for two weeks and then a prompt reappearance in spite of continuous use of the ointment. During this interval a similar eruption appeared on the trunk, particularly on the upper back and chest, and the mother called attention to an ulceration in the right groin which had appeared in the past two weeks. Severe constipation had been noted since the previous visit, and the mother had administered

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daily soap and water enemas, which in the past two weeks returned blood. Penicillin, administered for an "upper respiratory infection" in another city, had had no effect on the eruption.

Punch biopsies were taken of several scalp lesions and of one lesion on the back. Histologically, these areas showed a very thin epidermis beneath which there was a pronounced cellular infiltrate composed of closely packed reticular cells some of which had an indistinctly foamy cytoplasm. Sudan IV stains for fat were negative. The histologic diagnosis was non-lipoid histiocytosis.

A pedatric consultation was then arranged and the patient was hospitalized for further study in January, 1950.

On admission the temperature, pulse rate, and respirations were normal. There was a crusted seborrhea-like eruption on the scalp and a papular eruption on the trunk simulating keratosis follicularis. The right groin showed a silver-dollar sized, grossly infected ulceration. There was purulent discharge from the right ear and generalized lymphadenopathy. The liver was palpable 2 cm. below the costal margin and the spleen was enlarged 1 cm. below the costal margin.

Laboratory examination of the blood revealed the following: RBC 3,380,000; hemoglobin 9.8 gm; WBC 12,850; differential count, neutrophils 52, lymphocytes 47, eosinophiles 1, monocytes 9. The urine contained 120 mgm percent of albumin; no sugar; many leucocytes and bacteria. Bence-Jones protein was not present. Culture of the drainage from the right ear showed gram-positive staphylococci. Culture of the urine showed B. pyocyaneus. The non-protein-nitrogen was 39.5 mgm percent. The blood cholesterol was 303 mgm percent, with cholesterol esters 250 mgm percent. A roentgenogram of the chest showed an irregular fine mottling throughout both lung fields, more marked at the inner aspect of the bases Roentgen ray diagnosis was broncho-pneumonia, but a parenchymatous infiltration could not be excluded. Roentgenograms of the skull were normal.

Several transfusions were given in the hospital which improved the red blood cell count and hemoglobin. Penicillin, 25,000 units every 3 hours, and aureomycin by mouth did not alter the high white count or the urinary findings over a 10 day period. Liver, iron, and a low fat diet were prescribed.

The child was discharged unimproved 10 days after admission with the diagnosis of Letterer-Siwe disease.

Soon after leaving the hospital a tonsillar mass appeared which became ulcerated and gradually enlarged over a period of several months. Ulcerations appeared in the axillae and about the anus. The eruption on the scalp became much worse spreading anteriorly over the face, neck, trunk, back, ears, and into the ear canals. The finger-nails became dystrophic and brownish in color, and several dropped off. Hyperplastic lesions and ulcerations appeared on the gums, which bled easily. The liver became palpable 4 cm. below the costal margin and the spleen 3 cm. below the costal margin.

In August, 1950, the child was taken to Children's Hospital in Denver where the diagnosis of Letterer-Siwe disease was confirmed. Serum cholesterol taken at that time was 335 mgm. percent. Bone marrow studies showed only myeloid hyperplasia. Complete roentgenographic studies of the long bones and skull were negative. The white blood count was 25,300. The patient was given a 12 day course of cortisone, receiving a total of 1,150 milligrams. The only change noted was a slight improvement in the skin.

Six months after discharge from the hospital in Denver, the child was seen again in the office. At this time, he was taking 25 mg. of cortisone once every 10 days. He was severely jaundiced, with marked atrophy of muscles and the skin, and generally appeared moribund. The parents refused further hospitalization or treatment for the child.

DISCUSSION

Dermatologists in the past have paid little attention to the cutaneous manifestations of systemic reticuloendothelial granuloma. These include purpuric lesions, seborrhea-like lesions, papular eruptions of the trunk, scalp, axillae, and arms, of a yellowish or brown color, and ulcerations of the groins, axillae, and hard palate. Skin lesions are found most commonly in Letterer-Siwe disease and Schuller-Christain disease, altho both diseases may show no cutaneous lesions.

Characteristic findings in Letterer-Siwe disease, besides the skin manifestations, are splenomegaly, hepatomegaly, localized bone tumors (diagnosed by roentgenograms or at necropsy), secondary anemia, and generalized, painless lymph adenopathy. The patient presented here

showed all but the bone tumors which may have been present but undiscovered in the roentgenographic studies done. This disease occurs exclusively in infants. The onset is acute and the course progressively downhill to a fatal termination in a few weeks to several years. Histologic observations consist of a pronounced hyperplasia of non-lipid-storing macrophages in the organs affected, most commonly the skin, bones, spleen, liver, lungs, and lymph-nodes. Histo-pathologically, it is a non-lipid histiocytosis. The cause is unknown.

SUMMARY

A report is made of a case of Letterer-Siwe Disease with clinical observations and laboratory studies.

1. Laymon, C. W. and Sevenants, J. J.: Systemic Reticuloendothelial Granuloma, Arch. Dermat. and Syph. 57:873-890 (May 1948).

BASIC *Science* SEMINAR

BLOOD COAGULATION

Robert P. Waldmann, M. D.
Tucson, Arizona

BLOOD COAGULATION

Normally, five or six minutes after being collected from a person's vein, blood becomes jelled, forming a clot composed of a delicate network of fibrils in which are enmeshed the solid constituents of the blood. After approximately an hour this mass becomes shrunken and there has become expressed a clear straw colored fluid, called serum. If, however, instead of allowing the blood to stand, it is centrifuged immediately after it is collected, again a clear fluid is obtained. This is called plasma, and if left to stand, it too will clot and express serum. Consequently, one may surmise that the mechanism of clotting is a phenomenum of the plasma.

Classical Theory of Coagulation—

The classical theory of coagulation was offered in 1904 by Morawitz, Fuld and Spiro. The substances involved in the clotting mechanism according to this theory include prothrombin, thrombin, thromboplastin, ionized calcium and fibrinogen. By the action of thromboplastin, prothrombin becomes converted in the presence of calcium ions into thrombin. Fibrinogen then through the action of thrombin is converted into fibrin in which become entangled the erythrocytes, leukocytes and fragmented platelets, thus forming a clot. Simply, therefore, the classical theory is expressed as follows:

Prothrombin + Thromboplastin + Calcium Ions →Thrombin

Thrombin + Fibrinogen→Fibrin

Prothrombin—

Prothrombin is chiefly produced in the liver, but is also formed to a small extent in the bone marrow(1). The antihemorrhagic vitamin, vitamin K, discovered in 1934, is the governor of the production of this factor of coagulation. A deficiency of this vitamin was found to cause a prolonged coagulaton time. In 1936, it was shown that synthesis of vitamin K occurs in the intestine as the result of bacterial action(2) and therefore, it seems established that the immunity to a dietary lack of vitamin K is due to the synthesis of this vitamin.

Bile is required for absorption of vitamin K3 and the bleeding tendency occurring with obstructive jaundice is brought about by the failure of absorption of vitamin K since no bile is made available. In fact, any interference with its absorption may result in a tendency to bleed, as with sprue, liver disease, biliary or gastrocolic fistula, etc. Hypo-prothrombinemia induced by dicumoral or by salicylic acid, and the hemorrhagic tendency of the newborn, and cholemic bleeding may be eradicated by the administration of vitamin K.

However, the discovery of this vitamin's properties has not contributed to the understanding of the actual coagulation mechanism. Most advances made in the past fifteen years are due to the quantitative methods for determining prothrombin. The one-stage method of determination, simple, yet reliable, was utilized in bringing hypo-prothrombinemias under clinical control.

According to Quick and Stefanini 4 there are two states of prothrombin, free and precursor. For the precursor, prothombinogen, to become free, it must contact a roughened surface. Should this theory be correct, prothrombinogen could not participate directly in hemostasis since there are no rough surfaces intracorporally. Quick 5 indicates that free pro-

thrombin decreases readily with the administration of dicumoral while the prothrombinogen is not effected for several days. The two-stage method of determining prothrombin time measures total prothrombin whereas the one-stage method measures free prothrombin, and since free prothrombin decreases readily with dicumoral, the one-stage method would indicate a decreased prothrombin time several days early and, therefore, it may be concluded that only free prothrombin acts in the immediate process of hemostasis, and that the one-stage method of prothrombin time determination should be used to control hypo-prothrombinemia.

Thromboplastin—

Thromboplastin is believed to be present in all body tissue, especially rich in lung and brain tissue. Platelets were thought to be a rich source of thromboplastin as well. Therefore, when blood is shed, thromboplastin would conceivably be liberated from injured tissue and from fragmented platelets, thus initiating the clotting mechanism. However, Quick 6 found that instead of thromboplastin, platelets contained an activator which converted thromboplastinogen in the plasma into thromboplastin which then would react with prothrombin to produce thrombin. Thromboplastin was assumed by most authorities to be a catalyst. Mertz, Seegers and Smith(7) have shown that its reaction with prothrombin is a stoichiometric one, however. It has been suggested that thromboplastin is inactively present in plasma and becomes released on contact with a rough surface(8).

Calcium–

A low serum calcium is never a causative factor in hemorrhagic disease. In hypo-parathyroidism where the serum calcium may be depressed to less than one-half the normal value, the coagulation time is not lengthened. It has been generally accepted that ionized calcium is essential for coagulation. According to Quick and Stefanini(9) sodium oxalate when added to blood not only precipitates ionized calcium, but it also removes the calcium from a compound which is essential for coagulation, and that citrate added to blood combines with prothrombin rendering it inactive. Ther studies of prothrombin activity under various types of conditions suggests the presence of a labile factor which is indispensable for coagulation and unstable in decalcified plasma. Lovelock and Burch(10) state that calcium is not essential for the coagulation of blood and that the anticoagulant activity of oxalate and citrate can be explained as due to their ionic change. Calcium-free plasma is said to have clotted on a fivefold dilution, but not in the presence of fluoride or citrate ions; thus suggesting that it is the presence of these ions rather than the absence of calcium which prevents blood containing them from clotting.

Fibrinogen–

Fibrinogen is produced in the liver, and a defect of this substance is a rare cause of bleeding. In fact, hemostasis is possible in the absence of fibrinogen. There have been recorded a number of cases wherein there is a congenital lack of this plasma protein. Since these persons do not exanguinate–instead, tend to bleed even less than those with hemophilia–it may be concluded that coagulation does not depend on fibrin plugging.

New Concept of Blood Coagulation–

The old classical theory of coagulation leaves much to be explained as, for instance, the function of platelets, the actual source of thromboplastin, the auto-catalytic action of the coagulation reaction, correlation between coagulation and the mechanism of hemostasis.

Quick(5) has presented a new concept of the clotting of blood. He states that an enzyme, thromboplastinogenase, released by platelets, combines with thromboplastinogen from the plasma to produce thromboplastin; also that thromboplastin is obtained from injured tissue, as has been the general conception. The thromboplastin then, according to his theory, joins with the "prothrombin complex" of the plasma, which is made up of calcium, prothrombin and a "labile factor" to produce thrombin. Fibrinogen from the plasma then reacts with the thrombin to produce fibrin.

As stated before, Quick and Stefanini claim that prothrombin exists in two states, free and a precursor they call prothrombinogen, which to become free must contact a roughtened surface.

A " prothrombin labilizing factor" was demonstrated by Quick(11) when he was able to show that stored oxalated human plasma having an increased prothrombin time when mixed with plasma of a dog with hypo-prothrombinemia induced wth dicumoral resulted in a mixture with decreased prothrombin time. A factor gone in the stored plasma evidently was not the same

as that one decreased by dicumoral—consequently, prothrombin must have two components, one instable on storage and another adsorbable to aluminum hydroxide and similar agents. This discovery of Quick's is identical with "factor V" of Owren's(12). The labile factor, essential in thrombin formation, thus disappears in stored oxalated plasma, and, incidentally, like prothrombin, is inactivated at 60° C. Its quantity is determined by noting the amount required to bring the prothrombin time of stored plasma to a fixed value. According to Quick(13), this factor is not an accelerator, since an amount larger than the minimal requirement needed to produce thrombin from prothrombin will not speed up the reaction nor increase the amount produced.

Alexander, et al(14) have concluded that the labile factor is consumed in relation to the amount and the velocity of prothrombin conversion, and that this factor is not a catalyst but an actual reagent used in the process of prothrombin conversion.

A new agent was discovered in 1946 which is said to accelerate the activation of prothrombin into thrombin and is called "accelerator globulin"; it was concluded that this Ac-globulin is probably the same as Quick's labile factor (15, 16).

Therefore, blood contains in addition to classical prothrombin, a labile factor essential for production of thrombin, and dicumoral nor a deficiency in vitamin K effects its concentration. The action of this factor is not certain; it is claimed by some to be catalytic. Quick and Stefanini(17) say it has a stoichiometric action with other clotting factors to form thrombin and demonstrate that with a low labile factor, there is a comparative decrease in the production of thrombin, even with an increased thromboplastin, and, therefore, say:

Thromboplastin + labile factor + calcium + prothrombin → thrombin.

During coagulation, the conversion of prothrombin to thrombin occurs with increasing velocity—an autocatalytic phenomenon. Certain substances arising during coagulation accelerate, activate, or otherwise act as ancillary agents in the conversion of prothrombin to thrombin in the presence of thromboplastin and calcium—they include the serum Ac-globulin, Factor VI of Owren, Serum Prothrombin Conversion Accelerator (SPCA) of Alexander, Prothrombinkinase and Thrombinkinase of Milstone, and the Labile Factor of Quick. It is the opinion of Alexander et al(18) that these substances are alike; that any difference may be due to the difference in technique of study, in the purity and source of material, and in interpretation. They compared the properties of SPCA and serum Ac-globulin, and say SPCA accelerates the conversion of prothrombin to thrombin in the presence of a labile serum component. They believe that "serum Ac-globulin" is a mixture of at least two clotting components, plasma Ac-globulin and SPCA; the former being a plasma component and labile and SPCA being a serum factor, relatively stabile. The labile plasma Ac-globulin is probably identical with the labile factor of Quick and is essential for rapid prothrombin conversion. As SPCA is evolved during coagulation, the reaction is further accelerated, and it appears to Alexander that SPCA is the true "autocatalytic accelerator" of prothrombin conversion.

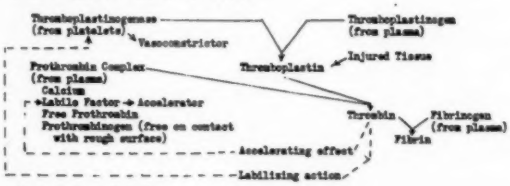
Stefanini(19) says that at first, thrombin is apparently formed slowly with the combination of thromboplastin, prothrombin, calcium and labile factor, but once enough thrombin has been formed, an auto-catalytic mechanism is set in motion with thrombin not only labilizing platelets which sets free the activator of thromboplastinogen, but also converting the labile factor into an accelerator which speeds up the formation of still more thrombin. This accelerator produced by the action of thrombin on the labile factor evidently is identical to factor VI, serum Ac-globulin and SPCA. It is pointed out by Stefanini that the different rate at which thrombin is produced in the presence of labile factor or accelerator explains why the formation of thrombin from prothrombin has been considered by some investigators to be a stoichiometric reaction, and by others, an enzymatic one.

It has been demonstrated that very little thrombin is produced when blood coagulates and that the thrombin is absorbed by fibrin, thus slowing the breaking down of platelets influenced by the thrombin; therefore countering the chain reaction(20). Thrombin, besides producing fibrin from fibrinogen, labilizing platelets to produce the thromboplastinogen activator and converting the labile factor into an accelerator, also causes platelets to liberate a local vasoconstrictor which acts on vessels in the surrounding area(21).

Thus, the function of the cloth is not to act as a plug, but to control the thrombinogenic reac-

tion and produce vasoconstriction by labilizing platelets. The fibrin acts only to delay the thrombinogenic reaction so that the platelets in the clot slowly disintegrate, and a gradual and prolonged production of the vasoconstrictor occurs. Carter and Warner(22) say that fibrinogen may protect Ac-globulin against various physical and chemical agents, and that it may inhibit Ac-globulin activity in the conversion phase of the normal clotting process.

Briefly, therefore, there are three phases in the new concept of blood coagulation. The first phase includes the formation of thromboplastin through the action of an enzymatic agent released by the platelets with thromboplastinogen in the plasma. The second prase is the formation of thrombin by action between prothrombin, thromboplastin, labile factor and calcium; the thrombin labilizes platelets leading to the production of more thromboplastin, and the thrombin also acts to convert labile factor into an accelerator agent (Factor VI, serum Ac-globulin, serum prothrombin conversion accelerator) capable of accelerating the formation of thrombin from prothrombin. The third phase is the reaction of thrombin with fibrinogen to produce fibrin and a clot.



Anticoagulants–

It has generally been believed that blood remains fluid in the vessels because thromboplastin in the circulating blood is of a very small amount and, therefore, thrombin is not produced and fibrin is not formed. Any small amount of thrombin in the blood is neutralized by an "anti-thrombin" present in low concentrations in the blood.

In 1918, Howell and Holt(23) obtained a powerful anticoagulant from extracts of liver they called "heparin". Lung, muscle and intestinal wall also contain heparin in large quantities. In serum, however, it is of negligible quantity, and believed not responsible for maintaining the fluidity of blood. Its anticoagulant properties are believed due mostly to its ability to inactivate thrombin; however, Ferguson(24) has shown evidence by experiments that heparin neutralizes the action of thromboplastin. According to Quick, heparin merely intensifies the action of the normal antithrombin of the blood to produce a powerful anticoagulant. Heparin is a product of mast cells, the mobile basophil cells of the tissues, clustered around the small vessels of tissues(25). Murray et al(26) state that besides prolonging the coagulation time, heparin hinders agglutination and deposition of platelets, discouraging formation of thrombin. Clinically, the most important use of heparin is in blood transfusions, operations upon vessels and preventing extension of certain types of thrombus, especially those conditions carrying the threat of fatal pulmonary embolism.

Considering other anticoagulants, biological substances besides heparin would include hirudin from the leech which like heparin, inactivates thrombin; dicumoral from spoiled sweet clover which depresses prothrombin concentration; peptone solution stimulating liberation of heparin from the liver; cobra snake venom. Neutral salt solutions as magnesium sulfate, sodium sulfate and sodium chloride, will slow coagulation but won't prevent it indefinitely. Azo dyes, as Trypan Blue, are powerfully anticoagulant. Coagulation may be prevented by de-calcifying the blood, as has already been discussed, employing the use of sodium oxalate or sodium citrate.

Hemophilia–

One of the hemorrhagic diseases is hemophilia, wherein according to Quick(27) there is a congenital lack of thromboplastinogen. The amount of hemorrhage is proportional to the decrease in quantity of this substance. If the circulatory system is intact, no hemorrhage occurs; however, the injury required may be very slight. In a well developed hemophilia, the coagulation time of the blood is greatly prolonged though the bleeding time is normal. There is usually no decrease in the number of platelets. It was generally believed that the essential defect was decreased thromboplastin due to abnormal stability of the platelets, and, therefore, a retardation of the conversion of prothrombin to thrombin, but Quick says this is not the case. The coagulation time test may be normal in mild cases. Any admixtures of tissue juice in the process of collecting the blood makes the coagulation test worthless. The prothrombin consumption test is a much more sensitive test than the determination of the clotting time(28). The clotting time does not

reach pathologic values until below thirty percent of prothrombin consumption. Quick also indicates that the prothrombin consumption test is of diagnostic value in this disease if the platelet count is normal, as only a small amount of prothrombin is used for coagulation since there is a definite decrease in the thromboplastinogen. Since prothrombin and thromboplastin react stoichiometrically, the more thromboplastin, the less prothrombin after coagulation. The thromboplastin available depends on the concentration of thromboplastinogen and platelets. According to Quick if there are over 100,000 platelets per c.m. of blood, the prothrombin consumption test is the measure of thromboplastinogen, but when the platelet count is low, thromboplastin is also decreased, and consequently, little prothrombin is converted. Also, the possibility that anti-thromboplastinogenase (inhibitor of the platelet enzyme) may be increased and causing a hemophilia-like disease must be ruled out.

The accepted treatment of hemophilia includes blood transfusion or direct application of tissue extract to the bleding point. Snake venom has also been usd, applying it directly to the wound.

Purpura–

Hemorrhage beneath the skin, from mucous membranes or into joints, commonly known as purpura, occurs in numerous diseases as scarlet fever, small pox, diphtheria, streptococcal infections; also scurvy, leukemia and certain anemias. It may occur with action of certain venoms, drugs and chemicals. Capillary fragility may be the primary cause in some types of purpura, whereas in others the defect may be a decreased number of platelets in the blood, according to the general belief. A reduction of platelets is not capable alone of inducing purpura; an injury to the capillary wall must coexist. A decrease in platelets may result from an increased destruction, or may be due to a decreased production as with leukemia or anaplastic anemia.

Thrombocytopenic purpura is treated surgically by splenectomy, which is usually followed dramatically by a prompt increase in platelets and frequently effects a cure. According to Troland and Lee(29) the spleen is the source of a toxic material which destroys platelets. They found that acetone extracts of spleens from patients suffering with thrombocytopenic purpura, when injected into rabbits, was followed by a prolonged reduction in platelet count. An abnormal number of megakaryocytes have been found in the bone marrow with an increase in the number of younger forms and it has been suggested that these magakaryocytes fail to produce platelets.

When the platelets are reduced as in this disease, there results a decreased amount of thromboplastin produced, since according to Quick (30), platelets are necessary for the activation of thromboplastinogen, and, consequently, little thrombin is produced, thus reducing the prothrombin consumption. It was generally believed that there was no defect in the coagulation mechanism since coagulation time is normal in this dsease. However, the actual hemorrhage is not due to a decreased number of platelets (though this fact does accentuate the bleeding), but, instead, to an increased permeability of the capillaries. It is not known whether this defect in the capillaries is due to a toxic agent or to the lack of a factor necessary for vascular tonicity. Quick and Stefanini(31) emphasize the importance of serum prothrombin activity not only in the diagnosis of hemophilia, but also in thrombocytopenia, where there is an impaired activation of thromboplastinogen. In either case, without activation of thromboplastinogen, thrombin can't be formed. The consumpton of prothrombin during coagulation is slight and consequently the very sensitive one-stage prothrombin consumption test is of diagnostic value. This test consists of adding thromboplastin, labile factor and fibrinogen to serum and measuring the clotting time of the mixture, this being a direct function of the prothrombin left unconverted in the serum. The one-stage prothrombin consumption test doesn't eliminate the accelerator effect, and, therefore, the test has been criticized as nonspecific. The diagnostic value of the test as pointed out by Stefanini and Crosby(32) is not compromised by the serum accelerator effect since it is not of such magnitude as to modify the results of the prothrombin consumption test to any extent.

Hemophilia-like Disease–

There exists a hemophilia-like disease which occurs in both sexes. Blood of a patient with this disease is believed to contain an inhibitor to coagulation since this blood when mixed with normal blood results in a mixture with a pro-

longed coagulation time; whereas, mixing blood of a patient with hemophilia with normal blood resulted n a mixture with a normal coagulation time(33). This inhibitor is believed to act on the thromboplastinogen activator(34). Blood transfusions are of no help in this disease. Evidently the inhibitor is in such a great concentration that it prevents even the new blood from coagulating.

Thrombosis–

Intravascular clotting may occur in the human body from several causes. It is doubtful whether such clotting occurs as a direct result of an increase in any of the elements of the clotting mechanism present in the circulating blood. Under certain circumstances, the probable factor is the liberation of thromboplastin with injury of tissue cells; however, the effect is confined to the region of the injury. A thrombus may be formed simply by clotting of blood in the usual way as occurs in an injured vessel. Also, cellular elements of blood may form a solid mass within a vessel independent of the clotting process as in smaller vessels when erythrocytes agglutinate as after a transfusion of incompatible blood. A true clot may then form in the stagnant blood column. Toxic thrombosis may occur with the arsenicals, mercurials, poisonous mushrooms, certain snake venoms, extensive burns, etc., but whether it occurs by injury to the vessel wall, destruction of blood elements or through their effects upon some phase of the clotting process is obscure. Infection is a common cause, destroying endothelium and liberating thromboplastin from injured tissue and disintegrated platelets, releasing its activator. Thrombosis of the veins of the lower limbs following operations upon the abdominal or pelvic organs is not uncommon—a cause for concern since there may be embolus formation.

Though the slowing of venous flow as with feeble heart action, confinement in bed, immobility of legs, low metabolic rate, etc., is probably the most important factor in the production of postoperative thrombosis, alteration in the blood itself following tissue injury including an increase in the platelet count, tendency for platelets to clump together, increase in amount of fibrinogen in the blood (increasing the sedimentation rate) undoubtedly favor the formation of a thrombus. Anhydremia also will encourage thrombosis. Therefore, prophylaxis should include early ambulation; encouragement of respiration to aid venous return, administration of thyroid extract to increase metabolism and circulatory rate, and of fluids to prevent dehydration; prescription of a high carbohydrate diet since high protein will increase formation of fibrinogen and platelets; administration of anti-coagulants (heparin, sodium thiosulfate, etc.).

Summary–

The classical theory set forth by Morawitz in 1904 and dominating the field almost to the present time represented a useful basis for studies of blood coagulation and the pathogenesis of hemorrhagic diseases; however, recent investigations have established significant findings that can't be reconciled with this old concept. Several new technical approaches have been made in the study of the clotting of blood which have helped considerably to make up for the shortcomings of the old theory, and allow for a better understanding and more accurate control of the hemorrhagic diseases, as well as offer a foundation for still greater achievements towards solving the true physiology of coagulation.

1. Drinker, C. K.: Am. J. Physiol. 41:5, 1910.
2. Almquist, H. L. and Stockstad, E. L. R.: J. Nutrit., 12:329, 1936.
3. Greaves, J. D. and Schmidt, C. L. A.: Proc. Soc. Exp. Biol. Med. 37:43, 1937.
4. Quick, A. J., and Stefanini, M.: The State of Component A (Prothrombin) in Human Blood; Evidence That It Is Partly Free and Partly In An Inactive or Precursor Form, J. Lab. & Clin. Med. 34:1203, 1949.
5. Quick, A. J.: A New Concept of the Clotting of Blood and the Hemorrhagic Diseases, J. Missouri St. Med. Assoc. 749, 1950.
6. Quick, A. J.: Studies on the Enigma of the Hemostatic Dysfunction of Hemophilia, Am. J. M. Sc. 214:272, 1947.
7. Mertz, E. T., Seegers, W. H., and Smith, H. P.: Prothrombin, Thromboplastin and Thrombin: Quantitative Interrelationship, Proc. Soc. Exper. Biol. & Med. 42:604, 1938.
8. Lenggenhager, K.: Irrewge der Blutgerinnungsforschung. Klin. Wschnsch. 15:1835, 1936.
9. Quick, A. J., and Stefanini, M.: Chemical State of the Calcium Reacting in the Coagulation of Blood, J. Gen. Physiol. 32:191, 1948.
10. Lovelock, J. E., and Burch, B. M.: Blood Clotting: The Inhibition by Anions and the Function of Calcium, Biochem. J. XXXIV, 1951.
11. Quick, A. J.: On the Constitution of Prothrombin, Am. J. Physiol. 146:212, 1943.
12. Owren, P. A.: New Investigation on the Coagulation of Blood, Arbok for det Norske Videnskopsakademi, 1944, p. 21.
13. Quick, A. J., and Stefanini, M.: The Concentration of the Labile Factor of the Prothrombin Complex in Human, Dog and Rabbit Blood. Its Significance in the Determination of Prothrombin Activity, J. Lab. & Clin. Med. 33:819, 1948.
14. Alexander B., Landwehr, C. and Goldstein, R.: Labile Factor of Prothrombin Conversion: Its Consumption in Normal and Abnormal Blood Coagulation, Federation Proc. 9:4, 1950.
15. Fantl, P., and Nance, M. H.: Activation of Prothrombin, Australian J. Sc. 9:117, 1946.
16. Ware, A. G., Guest, M. M., and Seegers, W. H.: A Factor in Plasma Which Accelerates the Activation of Prothrombin, J. Biol. Chem. 169:231, 1947.
17. Quick, A. J., and Stefanini, M.: The Concentration of Component A. in Blood, Its Assay and Relation to the Labile Factor, J. Lab. & Clin. Med. 34:973, 1949.
18. Alexander, B., Goldstein, R., and Landwehr G.: The Prothrombin Conversion Accelerator of Serum (SPCA): Its Partial Purification and Its Properties Compared with Serum Ac-Globulin, J. Clin. Investigation 29:881, 1950.
19. Stefanini, M.: Newer Concepts of the Coagulation of Blood, Bull. N. Eng. Med. Center XII: 51, 1950.
20. Quick, A. J., and Favre-Gilly, J. E.: Fibrin, A Factor Influencing the Consumption of Prothrombin in Coagulation, Am. J. Physiol. 158:387, 1949.
21. Zucker, M. P.: Platelet Agglutination and Vasoconstriction as Factors in Spontaneous Hemostasis in Normal, Thrombocytopenic, Heparinized and Hypoprothrombinemic Rats, Am. J. Physiol. 148:275, 1947.

22. Carter, J. R., and Warner, E. D.: Protective Effect of Fibrinogen on Accelerator Globulin, Proc. Soc. Exper. Biol. & Med. 74:388, 1950.
23. Howell, W. H., and Holt, E.: Am. J. Physiol. 42:328, 1918.
24. Ferguson, J. H.: Proc. Soc. Exp. Biol. Med. 42:33, 1939.
25. Skaud, W. O.: Arch. Physiol. 81, 1938; Supp. 15, p. 89.
26. Murray, D. W. G., Jaques, L. B., Perrett, T. S., and Best, C. H.: Surgery, 2:163, 1937.
27. Quick, A. J.: Pediatric Aspects of Hemophilia, Pediatrics, 3:312, 1949.
28. Soulier, J. P.: Study of Prothrombin Consumption. Practical Interest for the Diagnosis of Hemorrhagic Diseases, Acta Med. Scandinav. 137:1, 1950.
29. Troland, L. E., and Lee, F. C.: Bull. J. Hopk. Hosp. 62:85, 1937.
30. Quick, A. J., Shanberge, J. N., and Stefanini, M.: The Role of Platelets in the Coagulation of Blood, Am. J. Med. Sc. 217:198, 1949.
31. Quick, A. J., and Stefanini, M.: Activation of Plasma Thromboplastinogen and Evidence of an Inhibitor, Proc. Soc. Exper. Biol. & Med. 67:111, 1948.
32. Stefanini, M., and Crosby, W. H.: The One-Stage Prothrombin Consumption Test, Blood V, No. 10, 1950, p. 964.
33. Lozner, E. L.: Joliffe, L. S., and Taylor, F. W. L.: Hemorrhagic Diathesis with Prolonged Coagulation Time Associated with a Circulating Anticoagulant, Am. J. Med. Sc. 199:303, 1940.
34. Quck, A. J., and Stenfanini, M.: Activation of Plasma Thromboplastinogen and Evidence of an Inhibitor, Proc. Soc. Exper. Biol. & Med. 67:111, 1948.

PHOENIX *Clinical* CLUB

MASSACHUSETTS GENERAL HOSPITAL CASE NO. 36291

The Case History in this discussion is selected from the Case Records of the Massachusetts General Hospital, and reprinted from the New England Journal of Medicine. The discussant under Differential Diagnosis is a member of the staff of the Massachusetts General Hospital. The other discussants are members of the Phoenix Clinical Club.

First admission. A fifty-two-year-old bartender was admitted for repair of a right scrotal hernia.

The patient had been told that he had a "touch of gout" and a "skipping heart" for years. Physical examination, in addition to the hernia, showed an rregular heart rhythm, wth a rate of 80 to 90. Urinalysis was negative; the blood nonprotein nitrogen was 19mg., and the blood uric acid 2.7 mg. per 100 cc. The operation and convalescence were uneventful.

Second admission (Five years later). The patient was readmitted because of an attack of gross hematuria. He had been well in the interim up until one week prvious to this admission, when he noted easy fatigability and weakness. The right knee became swollen, and the urine was noted to contain gross blood. This lasted for four days.

He had had slight nocturia of some years' duration, but no frequency, dysuria or hesitancy. For two years he had exertional dyspnea with palpitation usually coming on after a heavy meal or on climbing stairs. There was no history of chest pain or ankle edema. Up until five years previous to admission for a period of six years there had been intermittent swelling of the knees, ankles and left great toe lasting from a few days to a few weeks. There was a history of heavy alcoholic intake up until two years previous to this admission. Physical examination showed a palpable, firm nodule in the right lobe of the thyroid gland, cardiomegaly, auricular fibrillation, a Grade III apical systolic murmur and a recurrent inguinal incisional hernia. The lungs, abdomen, extremities and prostate were negative.

The temperature was 99°F., the pulse 96, and the respirations 20. The blood pressure was 155 systolic, 110 diastolic.

Urinalysis showed a specific gravity of 1.005 and 10 to 12 red cells and 3 or 4 whte cells per high-power field in the sediment. Cystoscopy demonstrated a normal urethra and bladder. The ureters were easily catheterized, clear urine coming from each. A retrograde pyelogram disclosed a calculus in the region of the left middle calyx. After injection it was noted that this appeared to be in a cavity. The patient was discharged on the second hospital day.

Third admission (two months later). In the interval he was followed in the Out Patient Department. The serum calcium was 9.2 mg., the phosphorus 3.3 mg., the alkaline phosphatase 3.1 units, the total protein 6.8 gm, the uric acid 4.7 mg., and the nonprotein nitrogen 18 mg pe.r 100 cc. Guinea-pig inoculation of the urine was negative for tubercle bacilli. X-ray study of the chest showed the heart to be markedly enlarged in all chambers but more so on the left. A gastrointestinal series and x-ray examination of the neck were negative.

The patient had been passing small amounts of blood in the urine intermittently snce the previous admission. However, his strength and appetite were good. There were no new symptoms, and physical examination, an x-ray film of the chest, an electrocardiogram and laboratory data were essentially the same as at the previous admission.

Urinalysis on admission showed a specific gravty of 1.018, a+ test for albumin and 100 red cells per high-power field in the sediment. There were abundant colon bacilli and Staphylococcus aureus on culture. A urinary determination for cystine was negative, and a twenty-four-hour urinary specimen revealed a total calcium excretion of 48 mg.

On the sixth hospital day a nodule was excised from the right lobe of the thyroid gland under local anesthesia. The pathological report was nontoxic nodular goiter, with organized and canalized hematoma. He was discharged on the fifth postoperative day after an uneventful convalescence.

Fourth admission (seven months later). The patient had ben well except for one episode of passing dark-red blood in the urine for a few hours six weeks previously. A retrograde pyelogram showed a rounded calcium density overlying the left kidney measuring 7 mm. in its greatest dimension. The left kidney was slightly lower than the right and appeared slightly larger. On the left only the middle and lower calyxes filled. The calcium density appeared to lie within a major calyx, which came off close to the renal pelvis. The right ureter, pelvis and calyxes were normal. The hemoglobin was 12.8 gm., and the white-cell count 8000. Urinalysis showed a specific gravity of 7.012, a + test for albumin and an occasional red cell and 10 white cells per high-power field. Urine cultures were negative. He was discharged on the second hospital day.

Fifth admission (six weeks later). The patient had been well and had worked until a week previous to this admission. Then after passing "lemon-colored" urine he experienced chilly sensations followed by fever and malaise and accompanied by urinary frequency of once an hour, with some burning on micturition. This condition gradually abated over the next five days. For the twenty-four hours prior to admission he took one sulfonamide tablet every four hours, and on admission the symptoms had completely disappeared and the urinary frequency was every four hours. He believed that he had lost 10 to 15 pounds in the six weeks prior to admission. He was taking digitoxin, 0.2 mg. every day, and on this medication was no longer bothered by dyspnea or palpitation. There had been no recent attacks of joint pain.

Physical examination revealed slight distention of the neck veins, a moderately irregular pulse, cardiomegaly and a Grade II apical systolic murmur. The liver edge was palpable two fingerbreadths below the costal margin. There was moderate tenderness and voluntary spasm in the left upper quadrant of the abdomen to bimanual palpation. The right inguinal incisional hernia was easily reducible.

The temperature was 99°F., the pulse 94, and the respirations 25. The blood pressure was 130 systolic, 90 diastolic.

Examination of the blood revealed a hemoglobin of 13.4 gm. and a white cell count of 13,300. Urinalysis showed a specific gravity of 1.010 with a ++ test for albumin and innumerable white cells in the sediment. Culture of the urine grew a few colon bacilli. The nonprotein nitrogen was 37 mg. per 100 cc. An electrocardiogram and chest x-ray film were as before.

On the fourth hospital day the temperature was 101°F. The patient complained of pain in the right great toe, which externally appeared normal. Tenderness in the left upper quadrant to bimanual palpation was still present, and there was no costovertebral-angle tenderness. The white-cell count was 11,500, with 84 per cent neutrophils. On the following day the temperature was normal, and he felt well, but there was some swelling, redness and warmth of the right knee thought to be mainly periarticular The blood uric acid was 5.6 mg. per 100 cc., and the basal sedimentation rate was normal. An intravenous pyelogram was essentially similar to previous pyelograms except that on the left, in addition to a nonfilling superior calyx, there was incomplete filling of the middle calyx. Following 1 cc. of Mercuhydrin intramuscularly he lost 4 pounds in weight, the liver was no longer palpable, and the neck veins were less distended. By the thirteenth hospital day the temperature was normal, the knee was no longer swollen, and there were no subjective complaints. On the fourteenth hospital day an operation was peformed.

J. D. HAMER, M.D.

The case in question today concerns a 54 year old bartender who was reported to have several abnormal conditions; a nodular mass in the thyroid gland which later turned out to be a non-toxic adenoma after excision and pathological study; the findings of an enlarged, fibrillating heart, with a systolic mitral murmur which can be assumed to be rheumatic in origin,

and showing the signs and symptoms, at intervals, of moderate to mild decompensation. He had an inguinal hernia which was repaired, later tho, to recur; recurring flareups of arthritic symptoms in various tissues about the joints, either on a rheumatic basis, or, thought to be at one time, gouty in origin. Several uric acid determinations done during the several hospital admissions were within normal limits except at the time of his fifth hospital day, the value was recorded at 5.7 mgs. per 100 c.c. of blood.

The chief condition of interest, in this case, however, centered around the repeated admissions to the hospital because of episodes of hematuria, variable in amount and duration. Several studies were made for the purpose of finding the cause for the hematuria. A calculus was demonstrated on several occasions by pyelograms. It was found in the left kidney, and at the time of the later admissions, the urinary tract presented the signs and findings of an infectious process also. The patient was operated for some reason during his fifth admission. The record doesn't state whether the operation was done on the urinary tract, or for the purpose of repairing the recurring hernia again.

It is reasonably well established that the hematuria in this man resulted from some condition above the bladder, for we are told that the urethra and bladder were normal to cystoscopic examination. We then have to trace the origin of the bleeding in the prostate, the ureters, or one or both of the kidneys, or to some systemic process.

Of the systemic processes, it seems logical to exclude all of them, except that it is possible for the fibrillating heart to cause embolic infarctions in one or both kidneys, resulting in repeated attacks of hematura. Of the acute or chronic infections which at times cause hematuria, the possible presence of some degree of rheumatc fever, or possibly rheumatic endocarditis, (with renali infarctions) are the only conditions having any possible bearing on this case Such systemic diseases and general conditions as blood dyscrasias and leukemias, deficiency and dietary diseases (Scurvy, etc.); hematuria due to medications (Urotropin, sulfonamides, mandelic acid, salicylates, barbiturates and cantharides), and the diseases of unknown etiology, as (Hodgkins disease, periarteritis nodosa), and the nephrosclerotic kidneys, all seem to have no place in this man's difficulties as a cause for the hermaturia.

We must pass on then to a discussion of the intrinsic diseases of the upper urinary tract for the answer. Five major causes for hematuria are recognized: 1, calculus; 2, tumors; 3, tuberculosis; 4, infections other than tuberculosis; and 5, nephritis in one of its component entity forms. Pyelograms have previously demonstrated a calculus associated with the left kidney, seemingly sitting in a cavity of some causation, in this particular case.

What renal causes are there for hematura. We think of calculus, nephritis, tumor, (capsular or parenchymal); infection, acute or chronic, including tuberculosis, and anomalies of the kidneys, such as polycystc kidneys, pelvic kidneys, or horseshoe kidney, and trauma.

Of the causes of hematuria from the ureters, the same can be said, and, in addition, stricture and aberrant blood vessels, and from the prostate, we think of calculi, tumors, infections, tuberculosis and vascular engorgement.

Below this organ, there are other conditions not applicable here, associated with the baldder, bladder neck, and urethrae.

In this case, we have the presence of a demonstrated calculus and secondary infection at times. These conditions could be the source of the hematuria, but its quite difficult to imagine the judges' picking a case for discussion so easy of analysis. Was the operation done to remove the stone to prevent future hemorrhage? Could be—it has been done before. I have a feeling tho that the cavity in which the calculus seems to be embeded was of great interest to the clinicians. What could it be, a cystic tumor formation, a tuberculous cavity, a pyogenic cavity, a cyst from some type of rare infection, an abscessed infarct, or a ruptured adrenal gland tumor or infection encroaching upon or into the left kidney? The answer isn't clear from the record, except all studies for tuberculosis are reported to be negative. My own feeling causes me to place the cause of the hematuria in this case upon the presence of some type of transluscent new growth, with present of a calcification, in the left kidney.

ROBERT H. CUMMINGS, M. D.

I am uncertain as to whether I should thank Judge Dysart for allowing me the opportunity to discuss this case of renal calculus. My instincts cry out that pilfalls await the unwary urologist today.

Our patient is a fifty-seven year old bartender given to heavy alcoholic intake in the past, and who experienced acute attacks of arthritis of transient duration leaving, up till now, no permanent joint changes. These arthritic attacks involved the knee and great toe. The last attack was precipitated by, or was at least associated with, an acute urinary tract infection. This history together wth a suggeston of elevation of the blood uric acid concentration, leads me to believe that this man suffered from gout.

Likewise, he experienced periods of cardiac decompensation, requiring digitalis and mercurial diuretics for control. He was hypertensive, had an enlarged heart, but had reported normal electrocardiographic studies.

Lastly, he demonstrated hematuria on many occasions over five years. A calculus was detected in the left kidney.

The problem appears to me to be an attempt to relate these seemingly separate entities and to do so if possible.

Gouty individuals more commonly are hypertensive and show arteriosclerotic changes. In the case today the heart disease could be related to his gouty diathesis in the absence of evidence of thyrotoxicosis or a history of rheumatic fever. Persons with gout commonly pass renal calculi.

So far all seems straight forward but as I consider this renal calculus I have misgivings. Uric acid calculi are usually small, multiple, and non-opaque. This is a single calculus and is radio-opaque.

At this point it would be essential to see the x-rays, for without them I am at the mercy of the radiologist's reports. All physicians should personally review all x-rays, and this is especially important in urological work.

The first cystoscopy revealed a normal lower urinary tract, so the hematuria must have arisen from the upper urinary tract, where a calculus, size not stated, lay in a cavity in the region of the left middle calyx. Were I to see these films, I would attempt to decide whether this calculus lay in the cavity of the middle calyx or whether it lay in a cavity outside the middle calyx. If the former were true, the situation would not be unusual. But, a cavity outside the middle calyx brings up the question as to whether this cavity is a calyceal diverticulum, a congenital defect in which stasis occurs and in which calculi may form, or whether this cavity is a cortical abscess as found in renal tuberculosis. The calculus must be in a cavity connected with the calyx, for it was outlined on retrograde pyelography and thus intra-parenchymal calcification such as occurs in clear cell carcinoma of the kidney or hydatid disease is not possible. It should be noted here that evidence of acid fast bacilli in the urine was not found, and it may be assumed since this was never refuted that the cavity was not a tuberculosis cortical abscess. From the x-ray alone we may say that we have ruled out tuberculosis, clear celled carcinoma, and hydatid disease.

Nine months later a repeat retrograde pyelogram revealed a 7 cm. calculus seemingly lying in a major calyx and non-filling of the superior calyx was demonstrated. Were I to see these films I should like to know, was the kidney larger and lower than revealed by the previous films? Was the calculus in the middle calyx as implied in the first films, or was it blocking the superior calyx preventing its filling? This information is in those films and is denied me because of inadequate description and comparison.

On the last admission an intravenous pyelogram was said to be similar to the others except that now the middle calyx was incompletely filled. It thus appears that over ten and one-half months there was progressive blocking of the upper portion of the kidney, by an actively changing lesion not dependent upon change in size or position of the calculus alone.

I draw the following conclusions from this information: A calculus formed in the left kidney not because of excessive uric acid excretion, for their calculi are small and non-opaque. It formed rather because of stasis in one segment of the left calyceal system. It could have formed in a congenital calyceal diverticulum or as a result of blocking from another pathological process such as papillary neoplasm of the calyx.

Certainly the blockage of the superior and middle calyx resulted from a progressive lesion over a period of ten and one-half months, and the process could have been present as long as five years according to the history of hematuria.

I am reminded here of a patient I saw four years ago who had a left renal calculus in an upper calyx, who at the time of surgery showed an extensive squamous cell carcinoma of the pelvis of the kidney. This is a diagnosis that cannot be made before surgery, but is frequently

associated with calculi and chronic infection.

It is my belief that this gouty, ruptured individual with hypertensive arteriosclerotic heart disease had a left nephrectomy after treatment of cardiac decompensation. He probably survived the surgery, and the examination of the kidney comprises the pathological examination. I believe the kidney showed a calculus, associated with a transitional cell carcinoma, probably papillary, but possibly squamous cell carcinoma.

DIFFERENTIAL DIAGNOSIS

Dr. Richard Chute*: In this case it seems to me that we are dealing with three abnormal conditions—gout, heart disease and a renal lesion. I should like to start with the first two, and then discuss the renal lesion last.

There is no doubt that this patient had gout. The considerable period of years during which he had had intermittent attacks of swelling and pain in various joints, including the great toe, the steady increase of the blood uric acid to an eventual abnormally high value of 5.6 mg. per 100 cc. (normal, 2 to 4.5 mg. per 100 cc.), his age and his occupation (bartender), and his alcoholic history, all lead me to a diagnosis of gout. Tophi are not mentioned, but they occur in only about 50 per cent of cases of gout and therefore are not necessary to make the diagnosis.

Secondly, the patient went into congestive heart failure. Although hypertension was not a feature, the heart was markedly enlarged, suggesting longstanding inadequacy. Even though no history of rheumatic fever is given, enlargement of the heart, with a loud apical systolic murmur, is very suggestive of mitral-valve dammage with regurgitation. Also, auricular fibrillation is frequently associated with chronic rhumatic heart disease, especially mitral stenosis. Another possible etiology of the cardiac disturbance, although I do not believe that it has to be considered seriously in this case, is degenerative cardiovascular disease, which may be a complication of late gout and may lead to coronary or cerebrovascular accidents. The vascular lesions in gout are nonspecific and contain no tophi, but intracardiac tophi have been seen. However, in my opinion, the whole picture of this patient's cardiac trouble can be best explained on the basis of an old rheumatic heart disease.

Apparently, the nodule in the thyroid gland that turned out to be a non-toxic nodular goiter was noncontributory.

Now we come to the renal lesion. The patient has been known to have hematuria on and off for many months. Since the urinary bladder and urethra were normal, the evidence indicated that the blood came from the level of the bladder, and presumably from the pathologic-appearing and tender left kidney. Tumor in the urinary tract is the most frequent cause of hematuria, and when one is dealing with a patient in the cancer age (fifty-seven), malignant tumor is by far the most common source of blood in the urine. The loss of considerable weight during the six weeks prior to the last admission, despite the accumulation of fluid due to cardiac decompensaton, is compatible with cancer. However, he was not anemic, and it must be remembered that he was taking digitoxin, which might have cut down his appetite and thus his weght. Stone is also a not uncommon cause of hematuria, and has to be seriously considered in this case. Renal tuberculosis may causse bleeding, but that was thought of and pretty well ruled out by the fact that the guinea pigs inoculated with urine proved to be negative for tuberculous infection.

May we see the x-ray films, Dr. Wyman?

Dr. Stanley M. Wyman: The first chest film taken four years previous to the last admission shows a heart markedly enlarged, particularly to the left, probably in the region of the left ventricle and the left auricle. It pushes the esophagus posteriorly. The aorta is quite tortuous—in keeping with the known hypertension. The displacement of the esophagus is well demonstrated on a film taken three years later, this being due to the enlarged left auricle, which I think, as Dr. Chute has suggested, is quite consistent with rheumatic heart disease. There is some pulmonary congestion. The stomach reveals no intrinsic disease. There is a small diverticulum of second portion of the duodenum. The pyelograms were done over a period of approximately a year prior to the last entry, and they show a focal density on the left that measures 7 mm. in diameter. The original examination fourteen months prior to the last examination shows the kidney shadows to be fairly symmetrical; the upper pole of the left kidney, however, is not well seen. The calyxes of both kidneys are well outlined by the original retrograde examination, and some localized

*Associate visiting urologist, Massachusetts General Hospital.

hydronephrosis about the stone is seen. There are no other very gross changes. The last film, taken almost a year later, shows the left kidney to lie considerably lower in position than previously. At this time the upper major calyx fails to fill. It is impossible for me to outline the left kidney adequately, but its upper pole certainly seems a little fuller. The last examination by intravenous pyelogram shows essentially the same findings as the retrograde—namely, downward displacement of the left kidney and inadequate filling of the upper and middle major calyxes. I think it is worth noting that the lateral middle major calyx seems to be displaced on the retrograde and intravenous pyelograms when compared to the original retrograde examination.

Dr. Chute: Let us discuss what could give the picture of calcification and apparently a growing mass in the upper pole of this kidney. Of course, the perfectly obvious thing is tumor. Incidentally, tumors rarely have calcified flecks in them, but I think this picture is rather different from that. This calcified shadow is rather interesting in appearance because it is in a ring shape, which may mean calcification of either the splenic or the renal arteries or occasionally a renal aneurysm, which I think would be a little more medial in position. However, its position within the kidney outline suggests that it really was a stone. Tuberculosis might give calcification, but probably of a more diffuse or mottled character, and I doubt if it would cause a growing lesion in the upper pole. Another possibility is calcification of the wall of a cyst, but the cyst could also be seen. Another thing that probably would not produce calcification, however, is carbuncle of the kidney. This patient's hematuria over a good many months makes me believe carbuncle was not present. Calcified mesenteric lymph nodes are very common, but they tend to shift around and are characteristically mottled in appearance. Therefore, I shall make the obvious diagnosis and say that I believe this patient had a stone and also a kidney tumor, presumably renal-cell carcinoma.

Dr. Walter S. Kerr, Jr.: The kidney was easily palpable and was about three times the normal size.

Dr. Chute: That makes me feel happier temporarily.

CLINICAL DIAGNOSIS

Left-renal tumor.

DR. CHUTE'S DIAGNOSIS

Renal-Cell carcinoma.

Nephrolithiasis.

ANATOMICAL DIAGNOSIS

Papillary carcinoma of kidney, with lymph-node metastasis.

Nephrolithiasis.

PATHOLOGICAL DISCUSSION

Dr. Tracy B. Mallory: Dr. Kerr, I believe you operated upon this patient.

Dr. Kerr: It seemed most likely that the kidney contained a tumor, and we thought the most likely tumor was a renal-cell carcinoma as Dr. Chute did. The kidney was exposed and found to be very firm on its surface, and resection was carried out. Several enlarged lymph nodes near the aorta, one of which was over 1.5 cm. in size and was probably involved by tumor, were also removed.

Dr. Mallory: The upper pole of the kidney was swollen and very firm. On section a comparatively small papillary tumor was found in the upper calyx, which was continuous with an infiltration tumor mass, 6 cm. in diameter, extending through the renal substance to, and in one spot through, the capsule into the perirenal fat. A small abscess cavity with neurotic walls that communicated with the pelvis was present near the center of the tumor. Histologically, the tumor was a characteristic papillary carcinoma of transitional epithelium, but the degree of invasion of the renal parenchyma was unusual. A calculus about 8 mm. in diameter was present in the upper calyx. One of the lymph nodes showed metastasis.

Dr. Benjamin Castleman: Do you think the stone had anything to do with the tumor?

Dr. Mallory: Of course, in the gall bladder there is a very close association between gallstone and cancer. I do not know whether they have any similar relation in the kidney.

Dr. Fletcher H. Colby: I think the greatest concern about stone associated with tumor in the kidney is that the association is more likely if the stone lies within the renal pelvis than in the parenchyma.

Dr. Castleman: We have had 1 case* that I recall in which the patient had numerous stones in the pelvis and calyxes, leukoplakia of the pelvis, foci of carcinoma in situ and a frank squamous cell carcinoma.

*Case records of the Massachusetts General Hospital (Case 30442). New Eng. J. Med. 231:633-636, 1944.

THE *Secretary's* MESSAGE

AMA IN CHICAGO

LOUIS H. BAUER, M.D. OF HEMSTED, NEW YORK, IN DRAMATIC CEREMONIES IN WHICH HE ASSUMED THE PRESIDENCY OF THE AMERICAN MEDICAL ASSOCIATION DURING ITS 101ST ANNUAL MEETING IN CHICAGO, TUESDAY EVENING, JUNE 10, 1952, AIRED NATIONWIDE OVER ABC AND MUTUAL NETWORKS, DECLARED: "SLOWLY, BUT SURELY, WE ARE LOSING THE FREEDOMS GUARANTEED BY THE BILL OF RIGHTS"; "PERSONAL LIBERTIES ARE BEING TRADED FOR GOVERNMENT SUBSIDIES"; "THE GREAT DECISION—SOCIALISM OR AMERICANISM—MUST BE MADE BY ALL THE PEOPLE."

JOHN W. CLINE, M.D. OF SAN FRANCISCO, IN HIS FAREWELL ADDRESS AS PRESIDENT OF AMA SAID AMERICAN MEDICINE IS "STRONGER, MORE UNIFIED AND BETTER ABLE TO PREVENT THE DESTRUCTION OF THE HIGH STANDARDS OF MEDICAL CARE INEVITABLE IN SOCIALISTIC SCHEMES," AND MEDICINE HAS BECOME A SIGNIFICANT FORCE IN AMERICAN LIFE."

BARRING A REVERSAL IN THE NOVEMBER ELECTIONS AND A STRONG RECURRENCE OF THE THREAT OF SOCIALIZATION, THE COORDINATING COMMITTEE OF AMA NATIONAL EDUCATION CAMPAIGN, ORGANIZED IN 1948, REQUESTS DISSOLUTION BY THE END OF 1952. WHITAKER AND BAXTER, PUBLIC RELATIONS FIRM WHICH DIRECTED THE ACTIVITY, REQUESTS THAT THEY BE RELIEVED OF THEIR RESPONSIBILITIES AT THAT TIME.

PAUL DUDLEY WHITE, M.D. OF BOSTON MASSACHUSETTS, NOTED HEART SPECIALIST, SELECTED BY HOUSE OF DELEGATES AS RECIPIENT OF THE DISTINGUISHED SERVICE AWARD OF AMA FOR 1952.

E. J. McCORMICK, M.D. OF TOLEDO, OHIO, MEMBER OF THE BOARD OF TRUSTEES, VOTED PRESIDENT-ELECT OF AMA OVER F. F. BORZELL, M.D. OF PHILADELPHIA, SPEAKER OF THE HOUSE WHO RELINQUISHED THIS POST AT THE CLOSE OF THE CURRENT SESSION. JAMES R. REULING, M.D. OF BAYSIDE, NEW YORK, ELECTED SPEAKER.

REFERENCE COMMITTEE REPORT ADOPTED RECOMMENDING THAT THE BOARD OF TRUSTEES APPOINT A COMMITTEE TO STUDY AND CONSULT WITH THE AMERICAN OSTEOPATHIC ASSOCIATION REGARDING PERMISSION OF DOCTORS OF MEDICINE TO TEACH IN OSTEOPATHIC SCHOOLS; AND PRESIDENT'S COMMISSION ON THE HEALTH NEEDS OF THE NATION, HEADED BY PAUL B. MAGNUSON, M.D. WHICH UNDOUBTEDLY WILL BE REPORTED ON IN DETAIL BY OUR DELEGATE, MOST CONTROVERSIAL BUSINESS BEFORE HOUSE.

OUR EXECUTIVE SECRETARY ELECTED MEMBER OF THE EXECUTIVE COMMITTEE OF THE MEDICAL SOCIETY EXECUTIVES CONFERENCE.

WOMAN'S AUXILIARY TO THE AMA AGAIN CONTRIBUTES $10,000 TO THE AMERICAN MEDICAL EDUCATION FOUNDATION.

Editorial

ARIZONA MEDICINE
Journal of
ARIZONA MEDICAL ASSOCIATION, INC.

VOL. 9 JULY, 1952 NO. 7

CONTRIBUTORS

The Editor sincerely solicits contributions of scientific articles for publication in ARIZONA MEDICINE. All such contributions are greatly appreciated. All will be given equal consideration.

Certain general rules must be followed, however, and the Editor therefore respectfully submits the following suggestions to authors and contributors:

1. Follow the general rules of good English, especially with regard to construction, diction, spelling, and punctuation.
2. Be guided by the general rules of medical writing as followed by the JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION. (See MEDICAL WRITING by Morris Fishbein.)
3. Be brief, even while being thorough and complete. Avoid unnecessary words. Try to limit the article to 1500 words.
4. Read and re-read the manuscript several times to correct it, especially for spelling and punctuation.
5. Submit manuscript typewritten and double-spaced.
6. Articles for publication should have been read before a controversial body, e.g., a hospital staff meeting, or a county medical society meeting.

The Editor is always ready, willing, and happy to help in any way possible.

PAIN

There is probably no service which the average physician is called on more often to administer than the relief of pain. There is probably no service which is more appreciated by the patient and his loved ones. Certainly the relief of pain sometimes seems more welcome than the actual saving of a life and especially if the patient is having his life saved only to endure more pain. It is especially apropos then to note that the February 1952 issue of The Journal Lancet is devoted entirely to the discussion of pain.

John S. Lundy, M. D. of the Mayo Clinic is the guest editor for this issue and he has assembled a collection of papers on the subject of pain which is really informative and easy to read. A brief mention of some of these papers might be in order.

Dr. Lawrence C. Kolb discusses pain as a psychiatric problem and discusses a number of painful complaints with psychiatric components among which are painful phantom limb, drug dependency or addiction and hysteria. Dr. Eugene T. Leddy of Rochester, discusses the analgesic effect of roentgen rays and mentions that it is probably the method of choice in the relief of pain in acute sinusitis, acute bursitis of the shoulder, pain due to herpes zoster, pain due to psoriatic arthritis and pain due to secondary carcinoma of bone. Dr. Thomas J. Dry has a paper on thoracic pain and cardiovascular disease and includes in his discussion angina pectoris, pain of myocardial ischemia, myocardial infarction, pericardial irritation and disease of the aortic arch. Dr. Edward A. Banner in writing of pelvic pain from the point of view of a gynecologist discusses pain of ovarian origin, of uterine origin and pain originating in the oviducts. Pain-relieving drugs is the subject of the discussion by Dr. Ernest M. Hammes, Jr., of St Paul, Minnesota, and he divides the pain relieving drugs into four classes They are (1) those which act on the organ or tissue producing the pain such as cortisone in rheumatoid arthritis and ergot derivatives in vasodilatory headache; (2) those which act locally to block the conductivity of pain fibers, such as subcutaneous injection of procaine; (3) the true anesthetics which produce unconsciousness and thus relieve the awareness of pain; and (4) the analgesics, which selectively depress the central nervous system without loss of consciousness. Asprin and morphine are members of this last group. The relief of pain in surgical operations and obstetrics is presented by Dr. Ralph T. Knight of Minneapolis, Minnesota and a more detailed discussion

of diagnostic and therapeutic nerve blocks is given by Dr. John W. Pender and Dr. John S. Lundy who is the guest editor. The many possible causes of painful conditions in the upper extremity are well discussed by Dr. Collin S. MacCarty of Rochester, Minnesota. This is a particularly enlightening paper and is well illustrated. The last paper of the group is by Dr. Bayard T. Horton and is concerning histaminic cephalgia.

At Dr. Lundy's request, Dr. Thomas E. Keys of Rochester, Minnesota prepared a list of books and monographs on pain. There are about fifty mentioned on his list. There is also a section of digests from current literature on pain.

It may seem strange that such a detailed report should be given concerning a subject about which so much has already been said. It is our contention that not enough has yet been said. Almost every physician finds himself in a situation, at times, when regardless of how much he knows about pain it is not enough. It is our feeling, therefore, that this February 1952 edition of the Journal Lancet is a valuable edition to the medical literature and it is our hope that every physician will be encouraged to read it.

BOOK REVIEWS

ANTIBIOTIC THERAPY: By Henry Welch, Ph.D.; Charles N. Lewis, M. D. and Chester S. Keefer, M. D. The Arundel Press, Inc. Washington, D. C. 1951. Price $10.00.

This book fills a long felt need for the compilation of the essential authoritative and up to date information on the antibiotics all in one place for ready and quick reference. The first portion of the book is devoted to a historical sketch concerning the discovery of the various antibiotics and to a brief biographical sketch of their discoverers. The second section of the book deals with each antibiotic individually, giving the indications for its use, the indications for the anitbiotic and the dosage forms. The last section of the book deals with the individual diseases indicating the antibiotics which are most useful in their treatment and giving recommendations for dosage and administration in the light of the most recent knowledge. The antibiotics discussed in detail are tyrothricin, pencillin, streptomycin, dihydrostreptomycin, bacitracin, aureomycin, chloramphenicol, and terramycin. Also brief discussions are given on polymyxin, neomycin, mycomycin, viomycin and subtilin. There is a chapter on miscellaneous considerations of antibiotic therapy and this mentions such things as use of streptomycin and penicillin in the treatment of radiation damage. A very good bibliography is given and the index seems complete.

Surely any physician who has attempted to keep a file of information regarding the antibiotics will welcome this book as a delightful and most useful alternative.

R. L. F.

THE CHANGING YEARS. By Madeline Gray. Doubleday & Company, Inc. Garden City, New York, 1951. Price $2.75.

Every physician who has among his patients women who are in or near menopause will find in this book a means of answering the numerous would have time to give. Furthermore, it is questions which these patients have and answering them in more detail than the physician written in language which the patient can understand since the author is a laywoman, a patient herself. Her research has been careful and tedious and the average physician will find the information she has collected authoritative and reliable. He will find very little with which he can disagree. The attitude is frank, refined and optomistic throughout.

I feel that most physicians will enjoy reading this book and many of them will want to prescribe it for their patients.

R. L. F.

TOPICS OF *Current Medical* INTEREST

RX, DX, AND DRS.

By GUILLERMO OSLER, M.D.

TUBERCULOSIS THERAPY.—The Boston meetings of the National Tuberculosis Ass'n. and American Trudeau Society produced a few groans as well as cheers. Caution concerning isoniazid was partly balanced by nods of approval for certain types of surgery. . . . ISONIAZID (the official basic name for isonicotinic acid hydrazide) still produces amazing changes in symptoms of tuberculosis, notable nutritional improvements, and relatively little toxicity. The best (tho scanty) studies on resistance indicate that it occurs, often in 4 to 8 weeks, probably about as often as to streptomycin alone. (The other data on the drug are contained in profuse announcements by several drug companies). The major research will be aimed at finding a drug which will reduce the emergence of resistance to INH. It is known that INH penetrates body cells much better than does SM, and this may be a great eventual help. (Many of the items about this research have already reached print, due to a new gimmick of the American Review of Tuberculosis. Brief papers are published in the 'Notes' section, which can be put thru in 6 weeks instead of 6 months).

Late results from the tried-and-true THORACOPLASTY still show a solid two-thirds 'cured'. (The crippled chests don't show in the statistics, however). EXTRAPLEURAL PNEUMOTHORAX looks better because of the use of antibiotics, the scanty loss of lung function, and the probable future use of plastic sponge as a prosthesis. EXCISION is the glamour op., since the continuing reports show the procedure to be safe, definitive, and followed by more than 90 per cent conversion of infectiousness in certain series. The use of a replacement for lobes is being attempted.

The SANATORIUM was urged as being more necessary than ever for complete therapy. GENERAL HOSPITALS were urged to dash forward from their inertia and diagnose, admit, isolate, and care for patients with tuberculosis; it is a need, and it should be their function.

CORTISONE and ACTH have an unfavorable late or early effect on TB.

COLLAPSE THERAPY IN MENTAL HOSPITALS is being pushed, with permanent methods (thoracoplasty and excision) offering the best results and greatest constancy.

MEDICAL EDUCATION for graduates and undergrads is to be urged and subsidized. Few young physicians will start training as chest specialists unless they have tuberculosis—and fewer have it.

The release of ISONIAZID for sale in pharmacies and hospitals occurred on June 5th. . . . Pressure can not be given credit for the release, even tho the drug houses have a fat supply and the public demand has been ravenous. The plain reason is that its toxicity is negligible in therapeutic doses, and the questions of duration of effect, etc., are of no pertinent interest to the F.D.A. . . . This Osler regrets that it had to be done. Thousands of non-specialists will be using the drug widespread. Thousands of patients will receive it at home, evading a complete routine of treatment, remaining as infectious hazards at home, often developing a resistant bacillus, and ending up with a residual lesion which someone must later try to repair. . . . It is possible to use it wisely, but even the specialists who started to give it in January aren't sure how. Said Mowgli. "Look well, oh wolves!"

With drugs for tuberculosis being found less than perfect, with a huge series of drugs failing to cure arterial hypertension, peptic ulcer, and the common cold, we'd better not have bad news from the TOOTHPASTE front! The least we can expect is that the CHLOROPHYL stuff will control our halitosis.

The storm over the connection between CHOLESTEROL AND ARTERIOSCLEROSIS is subsiding enough so that one can see several details, says C. F. Wilkinson Jr. of New York. . . . Cholesterol can be manufactured by the body in large amounts. The blood level is affected only by extreme changes of diet except in a few metabolic disorders. Hypercholesterolemia is probably not a cause of atheromatosis. The physical state of cholesterol and other blood lipids seems to be important, as well as the interrelationship. Atheromatosis should be considered an episodic, intermittant, and cumulative disease, occurring (basically) at any age. . . . And, importantly, there is no lab test which can predict the lesion, either present or impending.

Drug houses have a strong argument in selling PENICILLIN FOR ORAL USE, other than the one of convenience. . . . Keefer and several others agree that the incidence of side reactions and hypersensitivity is less than from parenteral dosage. . . . With the new unbelievably low cost of the drug per million units (and how easy it is to remember when a million wasn't available in a good sized hospital), one can give it freely by mouth without selling the old homestead.

A. M. Smith writes a thoughtful article on enjoyment of old age in The Journal (Michigan). Under the title 'The Best of Life' he concludes that legislators have a long distance to travel before homes for the aged and ill and anxious and dispossessed are really 'homes'. We must try harder

and more constantly to give security and care and happiness to those elders who should be able to have them in the twilight years. . . . He quotes Browning on what the aged should be able to feel,—

Grow old along with me!
The best is yet to be
The last of life, for
Which the first was made.

The reluctance of many physicians to push a NEEDLE THRU THE ABDOMINAL WALL into the peritoneal space is not justified by the possible hazard, says C. M. Henry of Georgia. . . . Aspiration for diagnosis, intubation for ascites, insertion of air for diagnosis or therapy all require such a procedure, but the fact is that perforation of a hollow viscus is an almost impossible feat. "One has only to remember that both force and counterpressure are necessary to insert a much finer needle thru the bowel during intestinal suture."

The expansion of MEDICAL EDUCATION (to cost 250,000,000 dollars) has been hailed far and wide by the press. It should help solve the medical shortages which have been publicized, but it has a seamy side (all is not as it seems). . . . The increase in 5 years from an enrollment of 23,000 to one of 26,000 sounds easy, and not very large. The difficulty lies in being able to enlarge the classes of an individual school from 75 to 100, or from 100 to 150 students per class. The deans and faculty holler 'murder', especially in states where the legislature commands them to expand and then provides no funds.

The story of BLOOD TYPE IDENTIFICATION TAGS, as used in a state which leads in Civil Defense, is interesting. Michigan is about to have more than 800,000 people classified. . . . Several types of tags were devised, and the final tag is a combination of the best features. The tag is of plastic, rectangular, and with a hole in one end for a loop or chain. . . . One side is graphic and simple, with the international blood types in standard colors,—blue for group O, red for B, yellow for A, and white and black for AB. The public insists on this clearcut identification. . . . The reverse side has IBM transcriptions of several pieces of information on certain areas of the tag,— the name, blood type, Rh factor, year of birth, code number (for filing), accession number, and religion. . . . Two per cent of all typings were rechecked to determine accuracy, and an accuracy of 99.26% was found.

A paragraph on the BALLISTOCARIOGRAPH appeared here about 2 years ago. It must be updated now. . . . The principles have not changed, but the practice has. The cumbersome table model is now reduced to a small electromagnetic instrument, weighing 20 ounces, which is set up to be attached to the shins. The curves and interpretation are the same. . . . The cost is 35 dollars, and no other equipment is needed—except an electrocardiograph to which it must be attached.

An odd approach to therapy has been used in MENIERE'S DISEASE. (This condition is not to be confused with the syndrome). . . . The usual treatment attempts to cure a condition of the vestibule, either unilateral or bilateral. . . . Streptomycin was given in large daily doses (3 grams) with the object of abolishing vestibular function, but without acoustic damage. 'Cold caloric' response was used as the end point. . . . Five of eleven totally incapacitated cases were reported by Hanson (Ann. Otol., Rhin., and Laryng.) to be restored to employment, and the other cases attained comparable results.

Korea has provided a fine chance for STUDY OF CHEMOTHERAPY. It has also been a field-day for TERRAMYCIN. . . . Several diseases have been treated with several antibiotics, using rather large groups for each drug. Acute bacillary dysentery was effectively cleared by terramycin, aureomycin, or chloramphenicol, but the first was the best. . . . Acute amebic dysentery was also controlled by all, but terramycin seemed best.

One might stretch this column's inclusiveness and tell a SEMI-MEDICAL STORY, heard in Chicago from an officer in the A.U.S. Medical Corps. . . . He had just visited his relatives in the Ozarks, where a man's favorite dog rides beside him on the seat of a pickup truck, and his family rides in back. . . . Uncle Jake's favorite dog seemed to be ill with an intestinal infection. 'Doc' Ficklin, a neighbor with wide repute in such matters, was called in, nodded wisely, measured out two tablespoonsful from a bottle marked 'gasoline', and then watched the critter take off and race around the yard until he dropped exhausted on the ground. When he didn't stir, Jake inquired anxiously as to whether he was in danger. "Nope," said Doc, "just out of gas."

PROFESSIONAL BOARD
1951-52 Annual Report

During the fiscal year 1951-1952, the Professional Board held two meetings in Phoenix, Arizona; one on October 21, 1951 and the other on March 16, 1952. Dermont W. Melick, M.D., of Phoenix was recently appointed a member for term expiring in 1954, to serve as chairman. In line with recommendation of this Board, Council authorized a membership increase by one for a total of nine, and Elvie B. Jolley, M.D. of Bisbee was likewise appointed a member to serve for term expiring in 1954. With increasing activity and extension of scope of operations, it is the considered judgment of this

Board that a Sub-Committee on General Medical including diabetes, polio, geriatrics, general practice and industrial medicine will greatly facilitate deliberations on these subjects. Activation, thereof, is now in sight.

The Sub-Committee on Mental Health received Council commendation for its outstanding achievement in its undertaking of survey of conditions existing at Arizona State Hospital and submittal of a detailed report of its findings, cognizant of the tremendous amount of work entailed.

The Sub-Committee on Tuberculosis undertook a follow-up survey of all physicians in the state who had pneumothorax equipment in their offices with a view of determining those willing to care for ambulant cases discharged from the sanatorium. Efforts continued in cooperation with various agencies striving to increase the number of beds available for tubercular patients in Arizona on a county and statewide basis.

The Sub-Committee on Cancer has continued its cooperation with and functioned through the American Cancer Society, providing speakers for seminars and lectures, representation on Cancer Clinics and Detection Centers, and all other services including active participation in the administration of both the Service Program and functions of the Society.

The Sub-Committee on Maternal and Child Health continued its study of fetal and maternal mortality within the state and held numerous meetings for the purpose of reviewing voluminous records and statistics relating thereto, with a view of improving the situation through concerted action. With the sanction and approval of this Board, the Sub-Committee plans to expand its membership and act advisory to the Maternal and Child Health Division of the State Department of Public Health. It is anticipated a program of postgraduate education comprising refresher courses will be instituted and made available to all outlying districts within the state in an effort to accomplish a reduction in such mortality. Attention was directed to both the medical profession and the Arizona Hospital Association of the legal requirements governing Serological Tests for syphilis and opthalmia neonatorum procedure.

The Sub-Committee on Venereal Diseases reports the incidence of venereal diseases is definitely on the decline. Presently and for the immediate future, maintaining control is of paramount importance if such favorable progress is to continue. Routine Serological Tests for syphilis on pre-natals, as prescribed by statute, must be enforced and full cooperation of the medical profession to this end is essential. It is recommended that Council again go on record favoring a premarital examination law for this state which action is supported by this Board.

The Sub-Committee on Crippled Children in consultation with the Crippled Children's Section of the State Department of Public Health, established a working agreement with that Division eliminating further charges for medical services. Effective immediately, it shall be the policy of that agency to make one all inclusive per diem charge for institutional convalescent care based on the agency's classification of expenditures used for computing a per diem rate for reimbursement. This rate does not include a charge for medical care. The situation arose due to the increasing number of patients carrying poliomyelitis insurance.

The Sub-Committee on Hard of Hearing reports completion by the Arizona Society for Crippled Children, October 1, 1951, of a five-year survey in hearing conservation. A "testing program" has been established and continues in every county of this state through school or public health nurses or trained volunteer audiometrics. It is noteworthy to mention that trained women of the medical auxiliary of Gila County have undertaken as a project, speech and hearing clinics in its area under Society direction. Similar activity in other county medical auxiliary groups is being encouraged. Medical examinations by otologists in counties where available or general practitioners in outlying districts, as originally planned by the Association and local societies, continues with effective results. Otologists from the metropolitan centers go to the rural areas to examine children, and classes are attended by the local physicians. Effort is being concentrated in the educational follow-up of the children discovered with a hearing loss and are in need of acoutical training in speech correction through diagnostic speech and hearing clinics held in every county during 1951 and 1952. Children in need of acoustical training, the fitting of hearing aids, speech reading and speech correction are referred to one of the summer centers maintained by the Society (one each in Phoenix, Tucson and Flagstaff). A school for the pre-school deaf children, an important

educational medium in the follow-up of hearing conservation, has been developed in Phoenix by the Maricopa County Chapter for Crippled Children. Increased "testing" is desirable and it is the hope that soon there may be established in Phoenix and Tucson, hearing conservation centers possibly associated with the college and university in the respective areas.

The Sub-Committee on Seminars regrettably has had a year of inactivity due to the lack of a chairman. Now that the ranks have been filled it is anticipated that a course will be chartered for future activity.

Establishment of a program of support of qualified Arizona medical students in out-of-state schools by subsidy to such schools, comparable to agreements in effect in other states without medical institutions of learning, was previously recommended by this Board. Council directed its Legislation Committee to give consideration to the problem. It is gratifying to learn that progress has been made to this end and as of this writing the House of Delegates of the Twentieth Legislature of the State of Arizona in the Second Regular Session, effected a due pass on H.B. 266, an act ratifying and approving the compact for western regional cooperation in higher education entered into by the states of Arizona, California, Colorado, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington and Wyoming, and the territories of Alaska and Hawaii. This is at least the first step forward and it is the hope of this Board that before adjournment of the Legislature and meeting of our House of Delegates in Annual Session, the Senate will have taken similar action and the signature of the Governor will have been affixed thereto, completing its enactment into law.

The Arizona League of Nursing Education and the Arizona State Nurses Association have endeavored to develop a five-year plan for the improvement of nursing services in Arizona. Preliminary surveys have been completed and they now seek the assistance and advice of the medical profession and the Hospital Association in an effort to activate portions of the recommendations previously determined upon. With the support of this Board, Council has appointed a seven-man special committee to participate in further deliberations. It is expected a report of accomplishment will be forthcoming just as soon as the activities of this joint group get underway.

A Health Education Workshop at Arizona State College, Flagstaff, is being scheduled for August 18 through August 29, 1952. Your Board has arranged through the cooperation of the American Medical Association to have a representative of its Bureau of Health Education participate, satisfying request therefor received from the College.

The year has been replete with many miscellaneous problems which have been given thorough study and time consuming deliberation.

In behalf of the members of this Board, we wish to express our appreciation to the members of Council and House of Delegates of this Association for the privilege which was ours in serving the medical profession and the peoples of our state.

Respectfully submitted,
D. W. Melick, M.D.
Chairman — Professional Board

AMERICAN COLLEGE OF ALLERGISTS

PITTSBURG, PA. — Many allergic patients who, even as they seek relief, suffer severe reactions from pollen, mold and dust injection treatments, need no longer do so, according to Dr. N. E. Silbert, who spoke here today at the Eighth Annual Congress of the American College of Allergists.

Dr. Silbert, Chief of Allergy at Captain John Adams Hospital, Chelsea, Mass., said that the answer was an antihistamine, Chlor-Trimeton maleate. When combined with the injectable protein required for an allergy sufferer, this drug, he said, minimizes unfavorable side reactions in almost all cases. Thus, it enables the patient to tolerate high doses of the remedial protein (such as pollen extract), with the result that he can build up a far greater defense against the cause of his particular allergy than ever before.

SITUATIONS WANTED

GENERAL SURGEON — desires congenial association individual or group in Arizona. Well trained, experienced all phases general surgery. Just finished five years' residency; Part I Board; three years' general practice; five years' Army; Industrious, amicable, willing to work. Married; 39; Catholic. Eager to establish home in permanent location. Desire interview.

Write: Karl Kastl, M. D.; 422 Bryn Mawr Ave., Bala-Cynwyd, Pennsylvania.

Woman's AUXILIARY

CONVENTION REPORT OF THE PRESIDENT

Mrs. Royal Rudolph 1951-52

"A Way of Life," an address which was delivered to a Yale graduating class by the famous physician, Sir William Osler, impressed me years ago and impresses me more each time I read it. In it, he says, "The load of tomorrow, added to that of yesterday, carried today makes the strongest falter." His advice is, "Our main business is not to see what lies dimly at a distance but to do what lies clearly at hand. Life is a habit of day-tight compartments."

The living of this philosophy, if one may call it that, can mean, I think, broader usefulness and greater efficiency especially for us as members of the Medical Auxiliary. Never before has it been so necessary to shut out the apprehension of the future, the regrets of the past, and concentrate on the immediate need of service to a distressed world. That is what I would emphasize: that the more complex demands of today require a fuller, more concentrated form of service, which, I feel, our Auxiliary now stands ready to offer. It has been a matter of growth, day by day. I remember this organization twenty-five years ago when we were merely groups of doctors' wives meeting together in order to get better acquainted, helping with the various charities of our communities and, if you recall, paving the way for the gratifying sale of *Today's Health* by earnestly selling copies of the old *Hygeia*. Later, as we came to assume a more definite identity, we were called on to assist the Medical Association at conventions and to aid in promoting legislative measures approved by the profession. It is good to know we were ready and efficient as we dealt with what were then the immediate issues.

Today, times are different from the situation of twenty-five years ago, and the emergencies we have to meet were then undreamed of. But, if we are to keep pace, we must still crowd into our "day-tight compartments" that same readiness to serve and serve intelligently in capacities for which we as doctors' wives are particularly equipped. The threat of the freedom of enterprise which contronts every good American citizen bears a special threat, as you know, to the American Medical Association. Two years ago the Association launched the National Educational Campaign to preserve the American system of medicine. Although it has been attacked again and again by the advocates of Compulsory Health Insurance, it has steadily perserved until now the American public is coming to see that the medical profession is fighting for the health of the nation and the principle of scientific freedom which has made this country the world leader in medical progress.

In this campaign we are playing our part. The Medical Association openly recognizes that it is the members of the Women's Auxiliary, working at the grass roots, who have been greatly responsible for getting the true facts before the public. This is indeed a matter which "lies clearly at hand." So long as the wounded in Korea rely for aid upon those very measures for which we have worked so hard, we must remain vigilant.

From the reports, members in Arizona should feel proud of the past year's accomplishments:

1. Three new counties have been organized and membership increased.
2. Radio Health Education Program was promoted in 4 counties.
3. Nurse Recruitment was sponsored in 6 counties.
4. Nurse's Loan Committee gave financial aid to 3 girls.
5. Organized counties assisted 18 agencies financially or by volunteers.
6. Legislative Program disseminated much information to members.
7. *Today's Health* and *Bulletin* reported increased sales.
8. Articles in *Arizona Medicine* informed members of current medical topics.
9. Civil Defense chairman stood ready to aid communities.
10. A $50 gift was given to the American Medical Education Fund.

This is a magnificent program, but in the march of events we cannot rest upon our laurels. Our present contributions should be a spur to still fuller and richer contribution. We can

make it provided every member shapes her "way of life" to include her particular share, rather than let so few do so much. I realize only too well that our working months in Arizona are fewer than in some states; also, there are fewer women to assist many organizations. But that is all the more reason for us to remember the Auxiliary has only us, you and me, the doctor's wife, on whom to depend to carry out its program.

Before making my two suggestions for next year, which are not exactly new, I wish to call your attention to the fact that more and better material is continually being designed to help present the case of medicine to four important women's organizations whose endorsement is not yet on record. These groups are:

American Association of University Women
American Congress of Parent Teachers
League of Women Voters
Nurses' Association.

Gaining their approval is a major objective, and the combined help of the Women's Auxiliary is needed.

Because we now have an increased and better-informed membership, I feel that we can continue the work of the past year with even greater success, but I would like to recommend that we again include in our program the following:

1. Get the public schools to institute an essay contest, "Why We Should Preserve the Voluntary System of Medical Care in the United States," to stimulate the interest of pupils, parents and teachers in this issue.
2. Present information to the lay public by developing a Speaker's Bureau. The Auxiliary has women who have the ability to tell the story to local groups. Eventually this would affect the thinking of the community and lead to endorsement by national organizations.

These two suggestions, it has seemed to me are pertinent to the need that "lies closely at hand." Let us then follow Dr. Osler's philosophy and not clutter our lives with unimportant things. This year stands out as a very critical year in the welfare of our country. Can you think of anything more important now than to form the habit of including the work of the Medical Auxiliary in your "day-tight compartment"?

In closing, I wish to thank the officers, committee chairman, county presidents and all members of the Auxiliary for their loyalty and time so generously given and for the many courtesies extended to me during my visits to the counties. I have greatly enjoyed my term as president and feel my life has been happily enriched by pleasant memories of my association with all of you. I also wish to express my appreciation to the chairmen of this splendid convention, to the members of Maricopa County who helped to make it a success and to those who assisted with the art exhibit.

You are to have a new president, Mrs. Schoffman, who is prepared to be your guiding force. I hope you catch her earnestness and enthusiasm and that you will give her the loyal support that I have enjoyed. Success to you in 1952-53.

Respectfully submitted
Mrs. Royal Rudolph
Tucson, Arizona

DOCTORS' DIRECTORY

SANATORIUM DIRECTORY